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PREMORBID ADJUSTMENT AND CANNABIS USE IN FIRST-EPISODE-PSYCHOSIS PATIENTS A CROSS-EUROPEAN CASE-CONTROL STUDY

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Abstract

The harmful effects of cannabis use and possible neuropsychological impairment associated with its use are a contentious topic of debate in both research and public health, as is the fact that cannabis use has been repeatedly shown to be a risk factor for the development of psychosis.

Surprisingly, three different meta-analyses on cognition and cannabis, among schizophrenic patients, found better cognitive performance in patients with a lifetime use of cannabis (Potvin, Joyal, Pelletier, & Stip, 2008; Rabin, Zakzanis, & George, 2011; Yücel et al., 2012). This counterintuitive finding, coupled with the fact that most psychotic patients suffer from cognitive impairment (Reichenberg et al., 2009) make it more difficult to understand the relationship between these two risk factors.

Two different explanations have been advanced for this counterintuitive finding: a) a "premorbid-driven hypothesis" and b) a "neuroprotective-derived hypothesis". The latter explanation has gained greater support from the evidence that the CBD component has been useful as part of the treatment in several neurological disorders.

Cognition has been established as a predictor of real world community functioning in schizophrenia. However, studies on the relationship between cannabis use and neurocognitive functioning in psychosis, which have controlled for the potential bias of premorbid functioning, are rarely represented in this context and often inconclusive.

The main objective of the work presented in this Thesis was to explore this association in an epidemiologically-derived case-control study in a sample derived from *The European Network of National Schizophrenia Networks Studying Gene-*

Environment Interactions (EU-GEI) in order to test the first of these two hypotheses, with the aim of exploring IQ and premorbid conditions and how they are related to cannabis use in patients at their first episode of psychosis (FEP), by comparing those cannabis using patients to non-users and to their respective healthy controls.

The final aim of this work was to identify the relationship between IQ, premorbid social and academic adjustment with cannabis use in psychotic patients, compared to healthy controls, in order to be able to explain in which cases you can expect a better IQ and a better premorbid adjustment and why, by clustering the sample, first according to cannabis use and, secondly, to frequency of cannabis use.

I hypothesize the existence of a subgroup of patients with a recreational use of cannabis, who are less cognitively impaired at the onset and less socially withdrawn in the premorbid period than other patients.

The final sample of the present study included 1,895 subjects (834 cases and 1,061 controls), with complete information about cannabis use (CEQ) and premorbid adjustment (PAS) at least. 1,739 subjects in total had also complete information on their IQ (derived from WAIS-short version).

The study confirmed that patients who used cannabis in their lifetime with a recreational pattern of cannabis use have higher IQ scores and a better and more stable premorbid adjustment than other patients.

The study also suggested that the better premorbid social adjustment of patients with cannabis-use might be responsible for the contact with the substance and that cannabis use increased the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability.

Taken together, these results are able to rule out the alternative explanation of a neuroprotective role of cannabis use on cognition, in favour of the hypothesis of a complex relationship between premorbid predisposition and different pattern of cannabis use in determining this paradoxical result.

Acknowledgments

I have many people whom I am grateful for having help me in this work.

I want to start with Prof. Daniele La Barbera, who believes in me and sustains my professional career since 2004, when I wrote my first thesis with him. His empathic and smart presence as a master in my life was a professional example and secure place to come back after any learning period away from home.

Marta Di Forti, a such wonderful person and brilliant scientist who I thank for having stimulated and introduced me to the world of the research and to this topic, and who gave me the opportunity to go always a little ahead in my "zone of proximal development".

She welcomed me with her bright smile at King's College, where I had the honour to work with Sir. Prof. Robin Murray, who I am thankful for having supervised me in this work of thesis and during the first period at King's College, in 2011. He has stimulated my knowledges in the most kind, generous and attentive way anyone could desire and that might be unexpected by a so well-known and busy scientist.

This great experience of PhD was also surrounded from people without whom most part of this work could not exist. First of all, the whole EU-GEI research team of psychologists and psychiatrists in training from Palermo and across Europe, my colleagues of ever, Erika, Lucia and Alice who coordinated the EU-GEI team into the difficult "war system" of Palermo University. I want also to acknowledge that University of Messina gave the grant for my PhD.

Veronica Capuccio who supervised statistics with patience and professionality and a good dose of curiosity. Diego Quattrone, who helped me in cleaning the data, in constructing the database and in trusting that the work would have been right and

ready on time for the submission. They both have been always available, smart and funny travel companions.

I want to thank Charlotte Gayer Anderson and Prof. Craig Morgan who coordinated the cleaning effort and, last but not least, Prof. Jim Van Os who enthusiastically agreed to give a feedback and his supervision to this work and made possible the entire EU-GEI study.

Indeed, I had some very super-supervisors!

I am fully grateful to everyone of them and to all my loved people for supporting me all the time and I fully appreciate all patients and their families for the time they have given to us in a moment of pain of their lives. I really hope that our work could contribute a little to this field of research in order to improve their quality of life or maybe prevent their psychological suffering.

Presentation Letter - Sir. R. Murray

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and

Professors of the PhD Commitee

and

Prof. Daniele La Barbera
Tutor of Dr. Laura Ferraro

I strongly recommend the **PhD thesis** proposed by Laura Ferraro, titled "Premorbid Adjustment And Cannabis Use In First-Episode-Psychosis Patients - A Cross-European Case-Control Study" to your PhD Commitee for acceptance in its present form. It is a work of of high quality research, original, and interesting with respect to the further development of the field. Ms Ferraro was well motivated, hard working, and independent in writing it and my work as a supervisor has been very easy as I needed only to suggest minor corrections and amendments to her work.

The findings are of a quality more than satisfactory for publication and Ms Ferraro is already submitting part of her work to an international journal. Finally, her thesis has an European breadth and her study was partially conducted abroad, at King's College, under my supervision.

In conclusion, I have no hesitation in recommending Laura Ferraro's thesis be accepted for a "Doctor Europaeus" PhD qualification.

Yours sincerely

Sir Robin M Murray, FRS
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Presentation Letter - Prof. J. van Os

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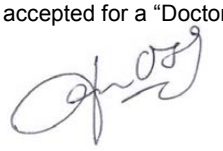
It is my great pleasure to recommend the PhD thesis proposed by ***Laura Ferraro***, titled “Premorbid Adjustment And Cannabis Use In First-Episode-Psychosis Patients - A Cross-European Case-Control Study” to your university's PhD Committee for acceptance in its present form.

In my opinion, the work in thesis represents solid epidemiological analysis of topical issues in the area of psychosis and substance use. The European Community is in dire need of this type of research in order to improve services and better plan preventive activities.

Laura worked very hard, quite independently and was quick in the uptake and implementation of feedback. She is indeed in the top 10% when it comes to absorbing academic issues and implement these in practice. I am sure this work will finds its way to academic journals of prestige - indeed part of the work has already been submitted.

Her thesis has an quite distinct European dimension; in fact, the work was carried out in part broad, in the UK, under the supervision of myself and Prof. Robin Murray.

In conclusion, I have no hesitation in recommending Laura Ferraro’s thesis be accepted for a “Doctor Europaeus” PhD qualification.



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Organization of the Thesis

This Thesis comprises a total of 6 chapters.

Chapter 1 is the introduction that covers, through an examination of the literature, the main topics of the thesis: the epidemiology of psychotic disorders and the risk factors associated with the development of psychoses; the concepts of premorbidity and Intellectual Quotient (IQ) and their characteristics in subjects with psychosis; cannabis prevalence and cognitive and premorbid characteristics of cannabis smokers with and without psychosis.

Chapter 2 describes the aims and the hypotheses of the work of thesis.

Chapter 3 presents methods, instrument and statistical analyses, along with the EU-GEI study and the study design.

Chapter 4 describes the results of a previous study about cannabis use and psychosis on a UK sample, (conducted in 2011 at King's College on a sample collected as part of the GAP study.

Chapter 5 summarizes the results of the study: the sample carateristics, data manipulations, results from the model and its progression by frequency of cannabis use and exploratory analyses.

Chapter 6 discusses the findings of the research project on the basis of the existing scientific data on the topic; it addresses methodological issues, strengths and limitations of the study and displays the conclusions.

Chapter 1

Definition of the Terms and Relevant Literature

1. Introduction

The harmful effects of cannabis use are a contentious topic of debate in both research and public health, especially in the context of its possible legalization and medicinal use. One of the most critical points concerns neuropsychological impairment, both specific and global, i.e. the impact of cannabis-use on individual psychological functions (memory, attention, executive functions), and its effects on the general Intellectual Quotient (IQ).

Another issue concerns the fact that cannabis use has been repeatedly shown to be a risk factor for the development of psychosis (Casadio, Fernandes, Murray, & Di Forti, 2011; Di Forti et al., 2009; Henquet, Murray, Linszen, & van Os, 2005; Moore et al., 2007; Potvin & Amar, 2008).

High efficiency, speed, and multitasking capacities are in great demand in today's world, and detrimental effects on brain functions have been identified as risk factors for different psychiatric disorders (Bora, Yücel, & Pantelis, 2010; Hatch et al., 2007) and for higher rates of mortality for different causes (Batty, Deary, & Gottfredson, 2007; Batty, Deary, & Macintyre, 2007; Calvin et al., 2011).

These considerations augment the significance and urgency surrounding the study of the problem of a probable detrimental long-term effect of cannabis on cognition, since cannabis is one of the most commonly-used illegal-drugs and the most widely-involved in the illegal market (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

The *National Survey on Drug Use and Health* in the United States, has identified cannabis as the leading drug associated with the initiation of illicit-drug use (Substance Abuse and Mental Health Services Administration, 2014). It also estimates that about 2.4 million people in the United States aged 12 or older had started using cannabis in 2012, and 5.4 million use marijuana on a daily basis (Substance Abuse and Mental Health Services Administration, 2014). Approximately 83.2 million of 15 to 64-year-olds adults in the European Union, are estimated to have tried this drug at least once in their lifetime (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

European Monitoring Centre for Drugs and Drug Addiction Use reports that its use is higher among young adults (aged 15-34 years) than in other age ranges, with almost 16.6 million individuals having used cannabis in the last year; Europe has seen an increasing number of people seeking treatment for cannabis-related problems (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

All this data suggests that a significant proportion of young people are at risk, and are using or abusing cannabis during one of the most critical periods of their brain development, i.e. adolescence.

While several studies report an acute adverse effect of cannabis on cognition, with obvious consequences on personal and public health, for example motor vehicle collision risk (Asbridge, Hayden, & Cartwright, 2012; Kalant, 2004), the long-term effects of cannabis use on cognitive functioning are still unclear (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Schreiner & Dunn, 2012). This state of uncertainty is mostly attributed to the difficulty in controlling for relevant variables—first of all, premorbid cognition—in naturalistic designs, thus preventing the drawing of firm conclusions about the casual direction of positive results.

To further complicate the matter, studies on cannabis use and cognitive impairment associated with schizophrenia have yielded controversial results. Three different meta-analysis have reported that among patients with psychosis, those who have used cannabis show better cognitive performance than those who have not

(Potvin, Joyal, Pelletier, & Stip, 2008; Rabin, Zakzanis, & George, 2011; Yücel et al., 2012).

Two different explanations have been advanced for this finding. The first suggests that those psychotic subjects who use cannabis have less premorbid cognitive impairment than those who do not. This could be because good premorbid functioning is necessary to acquire and sustain an illegal drug habit (Joyal, Hallé, Lapierre, & Hodgins, 2003; Rodríguez-Sánchez et al., 2010; Stirling, Lewis, Hopkins, & White, 2005) or because cannabis use increases the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability (de la Serna et al., 2010; Ferraro et al., 2013; Leeson, Harrison, Ron, Barnes, & Joyce, 2011; Løberg & Hugdahl, 2009; Schnell, Kleiman, Gouzoulis-Mayfrank, Daumann, & Becker, 2012; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009; Yücel et al., 2012).

A second possible explanation, based on research into animal models of Parkinson's disease and Alzheimer's disease, suggests that some cannabinoids have a neuroprotective action (i.e. CBD) (Binukumar et al., 2015; Chung et al., 2011; Gómez-Gálvez, Palomo-Garo, Fernández-Ruiz, & García, 2016; Martín-Moreno et al., 2011; Ramírez, Blázquez, Gómez del Pulgar, Guzmán, & de Ceballos, 2005), which may help to prevent psychosis-related cognitive decline (Jockers-Scherübl et al., 2007; Løberg & Hugdahl, 2009).

In this work of Thesis, I am going to test the first of these two hypotheses, by exploring conditions in the premorbid phase of psychosis, as I believe that they are a very good starting-indicator in determining the observed effects of cannabis on cognition among clinical and non-clinical samples.

2. Psychosis

Emil Kraepelin (1919) first collected under the term *dementia praecox* some conditions such as hebephrenia, catatonia and paranoia, characterized by an early onset, an apparently deteriorating course with cognitive impairment, delusions,

hallucinations and emotional flattening, and distinguished this condition from manic-depressive psychosis.

Then, Eugene Bleuler (1911) coined the term schizophrenia from the Greek words *schizein-frenos,* that means "separating-mind", to highlight the "splitting" of the major psychic functions. He indicated primary symptoms such as autism, associative disturbance, affective blunting and ambivalence, and secondary symptoms, that is delusions and hallucinations.

Kurt Schneider (1950) characterized schizophrenia by specific hallucinations (i.e. commenting voices or arguing voices), thought interference (i.e. thought withdrawal, insertion, broadcasting), and the experience of impulses or acts believed to be under external control (Schneider's first rank symptoms).

In the nineteenth century, the term psychosis indicated a heterogeneous group of diseases characterized by a loss of contact with reality, perceptual abnormalities such as hallucinations, thought disorders, cognitive impairment, emotional disorders, lack of insight and motor and behavioural abnormalities. Although many definitions of psychosis have been proposed, the diagnostic confines of schizophrenia and other psychosis remain ambiguous and the categorical distinction between schizophrenia and bipolar disorder is unsatisfactory, because of the incomplete knowledge about the aetiology and the pathogenesis of these disorders. In fact, schizophrenia merges on one side with bipolar disorder and on the other with schizotypal and paranoid personality disorder (Murray & Dean, 2008). People affected by psychosis may show a marked affective component and such conditions are often defined as schizoaffective disorders, but is not infrequent that their diagnosis stay unstable for the rest of their life.

The *International Classification of Diseases*-ICD (World Health Organization, 1992), and the *Diagnostic and Statistical Manual of Mental Disorders*-DSM (American Psychiatric Association, 2013) have furnished operational diagnostic criteria for schizophrenia. They differentiate psychotic disorders according to the type and duration of symptoms and to the presence of affective symptoms with some differences, i.e. the ICD-10 classification requests one month of psychotic

symptoms to make a diagnosis of schizophrenia, while in the DSM 5 recommends a duration of symptoms of six months, at least.

Nowadays, a new *continuum* diagnostic model is emerging, based on findings on psychotic-like symptoms that can be experienced by the general health population, with a median annual incidence of 2.5% and a prevalence of 7.2%, most of which are transitory and disappear over time (Linscott & van Os, 2013; J van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

Some studies show that first degree relatives of patients affected by a psychotic disorder have a higher probability to show paranoid, schizoid or schizotypal characteristics, together with some impairments in cognitive performance at an intermediate level between patients and normal controls (Murray & Dean, 2008).

2.1. Epidemiology

McGrath and colleagues (2004), in a systematic review of more than 100 large epidemiological sudies from 32 countries, reported a median incidence rate of schizophrenia of 15.2 per 100,000 persons *per year*, with a great variety between locations, thus replacing the notion that the incidence of schizophrenia doesn't vary much.

Schizophrenia onset is frequently placed in late adolescence or early adult life. Males have an earlier onset of schizophrenia than women and show a peak of incidence between 20 and 24 years while females show a peak between 29 to 32 years, with a larger number of cases presenting later in life (Castle, Sham, & Murray, 1998).

2.2. Risk Factors for Psychosis

Schizophrenia is 1.4 times more common in males than in females (Aleman, Kahn, & Selten, 2003; McGrath et al., 2004); urbanization increases the risk (Allardyce et al., 2001), the larger the town and the longer the individual has lived there, the greater the risk (Krabbendam & van Os, 2005). Immigration has a similar impact in males and females (Cantor-Graae & Selten, 2005), socio-economic

inequalities (Boydell, van Os, McKenzie, & Murray, 2004), perinatal complications, such as hypoxia (Cannon, Jones, & Murray, 2002), maternal exposure to stressful life events (Jim van Os & Selten, 1998; Verdoux, 2004), infectious agents (Brown & Derkits, 2010), maternal vitamin D deficency (Eyles et al., 2009) etc. are also risk factors, some more widely replicated than others.

Other earlier risk factors are childhood abuse and discrimination (Read, van Os, Morrison, & Ross, 2005; Stilo et al., 2013) parental loss or permanent separation from parents before age 16 (Craig Morgan et al., 2007) and childhood adversities in general (Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013; Varese et al., 2012). Other risk factors can occur later in life; a recent meta-analysis of 16 studies confirmed a positive association between adverse adult life events and onset of psychotic disorder with an overall weighted odd ratio of 3.19 (Beards et al., 2013).

Social adversities are thougth by some to act in cumulative way e.g. being unemployed, single, living alone, having poor education and having no close friends are associated with an increased risk of psychosis (C Morgan et al., 2008; Stilo et al., 2013). This may be mediated by the effect of an influence of stressful events on the hypothalamic-pituitary adrenal axis HPA and subsequently on the dopamine system, or it might be a genetic-environmental interaction between stress and genetic susceptibility (Howes & Murray, 2014).

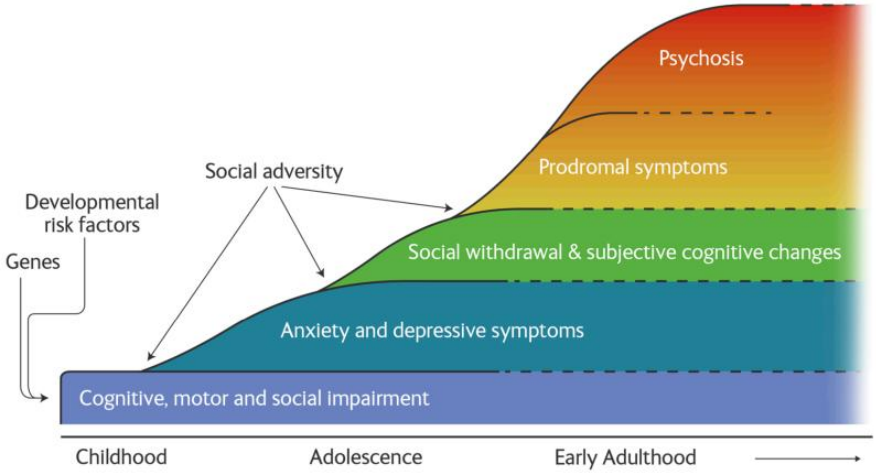
People who develop schizophrenia tend to show subtle cognitive, social and motor impairments in childhood. This is often followed, in adolescence/early adulthood, by anxiety, low mood and social withdrawal, and then the emergence of prodromal symptoms of psychosis leading to the onset of the first psychotic episode (**Figure 1**) (Howes & Murray, 2014).

Risk factors such as cognitive impairment, premorbid lower adjustment and drug consumption will be further discussed, as they are of crucial interest in this work.

Almost all of the environmental risk factors affect quite a large proportion of the general population, but presumably only a minority of exposed people with some genetic vulnerability will develop psychosis. In fact, schizophrenia is under considerable genetic influence.

A recent multi-stage schizophrenia genome-wide association study of 36,989 cases and 113,075 controls has identified 108 independent associations spanning conservatively defined loci that meet genome-wide significance. These are enriched among genes expressed in brain and in tissues that play important roles in immunity (Ripke et al., 2014).

Figure 1. The Trajectory to Schizophrenia Showing the Evolution of Symptoms and The Main Risk Factors (Howes & Murray, 2014).



Legend: people who develop schizophrenia tend to show subtle cognitive, social and motor impairments in childhood. This is followed, in adolescence/early adulthood, by anxiety, low mood and social withdrawal, and then the emergence of prodromal symptoms of psychosis leading to the onset of the first psychotic episode. Some risk factors play a role early in life, whilst others can interact with predisposing factors later in life. This figure is taken for exemplificative purposes from Howes, O. D., & Murray, R. M. (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*, 383(9929), 1677–87.

3. Premorbid Adjustment

Premorbidity is generally considered as the condition before the start of psychological or physical diseases. It is often used in relation to psychological function (e.g. premorbid personality or premorbid intelligence).

Premorbid traits are important because they could be associated with adjustment and/or recovery from an injury or illness. In fact, other usage of this term in psychology includes premorbid adjustment which has important implications for the prognosis of mental illnesses such as schizophrenia (Bernstein, 2006).

The best way to know premorbid function is via longitudinally planned observations. Otherwise, data concerning premorbid conditions can be collected retrospectively, through clinical interviews with patients and their family, anamnestic notes or clinical records. Premorbid personality, for example, refers to patterns of thinking, interpreting, and understanding oneself relative to the environment, existing prior to illness or injury and there is evidence that lifelong personality traits persist even after a traumatic brain injury (Frank, 2011). It means that this kind of assessment could be useful in many circumstances where it is important to know individuals' characteristics before planning treatments.

In the research field and in the clinical ground, ICD-10 (World Health Organization, 1992) and DSM 5 (American Psychiatric Association, 2013) are the most widely-used diagnostic systems to assess personality disorders, by providing a common language among colleagues. While the ICD is approved by the World Health Assembly, composed of the health ministers of all 193 WHO member countries, the DSM is agreed by the assembly of the American Psychiatric Association. Despite some differences, they both are expected to be atheoretical and research-supported.

Premorbid cognitive functioning is even more difficult to be measured. First of all, cognition embraces simple to complex mechanisms of the thinking process, such as perception, attention, comprehension, reasoning, linguistic procedures etc. But also understanding thoughts, empathising with others and further meta-cognitive abilities.

Intelligence is a concept that has born along with psychometric studies, which tried to condensate it into a model of Intellectual Quotient (IQ). IQ is often expressed with a measure from a test and which is not only a complex proxy for cognitive functions, but also one for social adaptation, environmental factors and genes (Wechsler, 1939). It is far from exhaustive of or independent from these other measures and, at the final end, is determined by a consensus on conventional and standardized samples of behaviour (Kaufman & Lichtenberger, 2006).

4. Intellectual Quotient (IQ)

Psychometric studies developed throughout the 1930s and into the early 1950s, in two different main directions: the construct of global and composite indexes (scales able to originate IQ scores) and analytic measures of specific dimensions (mental batteries).

The *Stanford-Binet* test first introduced the concept of IQ (Terman & Merrill, 1937), as a revision of the *Binet-Simon*'s test for children (Binet & Simon, 1916) and covered areas of reasoning, vocabulary and problem solving.

In this context, David Wechsler developed some new scales for measuring intelligence, defined as «the global capacity of a person to act purposefully, to think rationally, and to deal effectively with his environment» (Wechsler, 1939).

In his view, intelligence is a function of the entire personality and it is influenced by other non-intellectual factors, such as anxiety, perseverance and goal-directed behaviour; in fact, individuals who perform similarly in intellectual tests, do not cope identically with their environment, and part of the variance of the tests remains unexplained in factorial analyses.

The *Wechsler Adult Intelligence Scale* was developed first in 1939 (Wechsler-Bellevue Intelligence Scale - WAIS; Wechsler, 1939) for individuals aged 16–90 years, and was revised in 1981 (WAIS-R; Wechsler, 1981), 1997 (WAIS-III; Wechsler, 1997) and 2008 (WAIS-IV; Wechsler, 2008). From the WAIS was derived –In 1949– the *Wechsler Intelligence Scale for Children* (WISC; Wechsler, 1949) aged between 6 and 16 years.

WAIS-III provides scores for Verbal IQ, Performance IQ and Full Scale IQ, along with four secondary theoretical indices that do not contribute to the IQ calculation (Verbal Comprehension, Working Memory, Perceptual Organization and Processing Speed) so resulting in a test able to measure different content areas with both an overall score and a score for each content area differently related to the general factor (**Figure 2**; **Figure 3**) (for further details see Taub & Benson, 2013).

Figure 2. WAIS-III Hierarchical Measurement and Scoring Model (Taub & Benson, 2013).

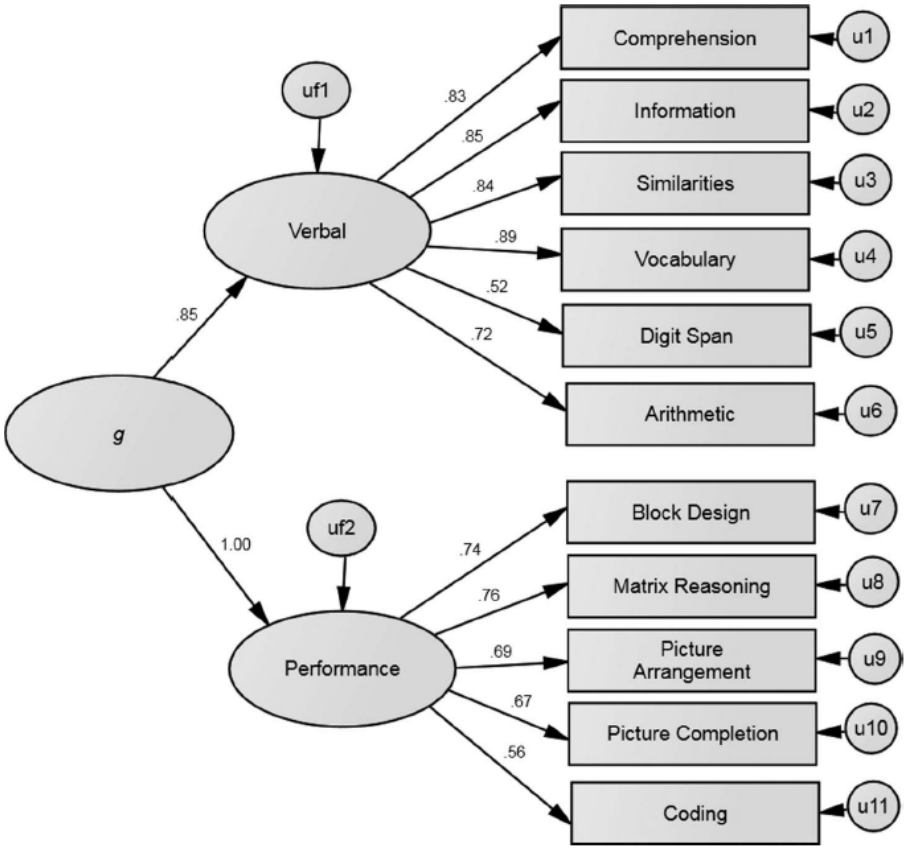


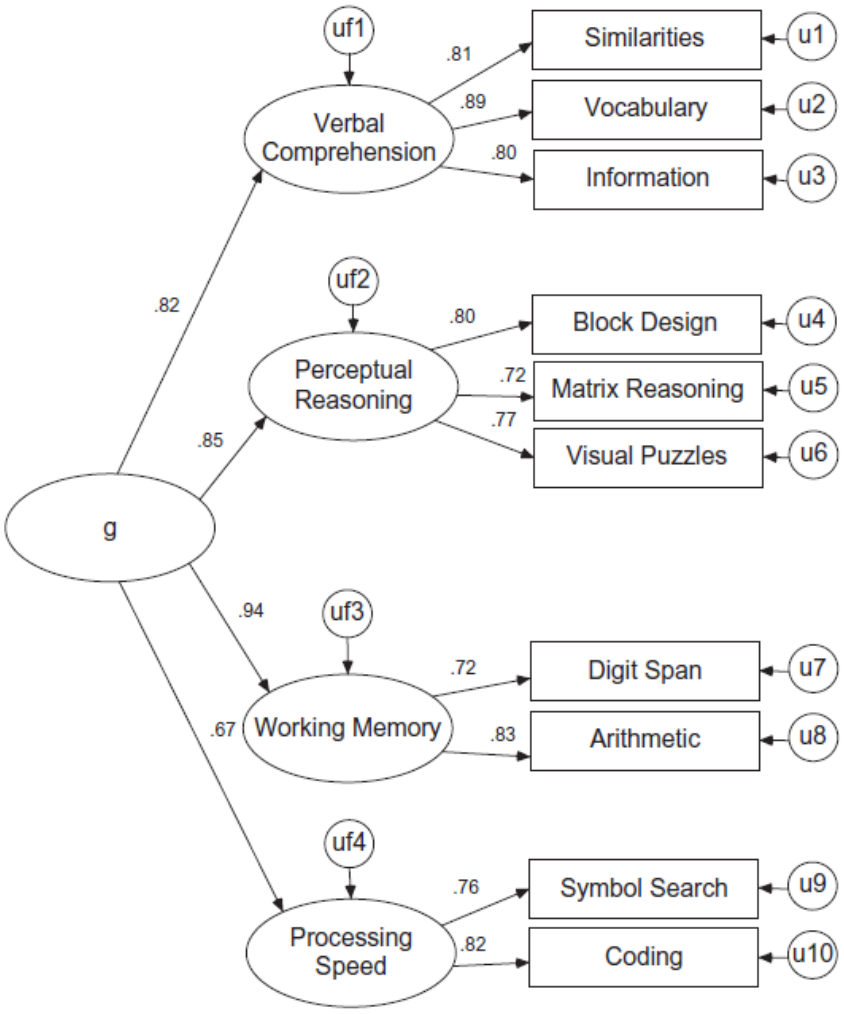
FIGURE 1 WAIS-III scoring measurement model.

Legend: The 11 subtests, contributing to an individual's FSIQ are presented on the right side. These 11 subtests are then subsumed by one of two first-order factors: Verbal IQ (VIQ) or Performance IQ (PIQ). The VIQ and PIQ are subsumed by a general factor of intelligence or FSIQ.
This figure is taken for exemplificative purpose from: Taub & Benson (2013). Matters of Consequence: An Empirical Investigation of the WAIS-III and WAIS-IV and Implications for Addressing the Atkins Intelligence Criterion Historical Overview. *Journal of Forensic Psychology Practice*, 13, 27–48.
Abbreviations: *g*: general factor; uf1-uf2: first order factors; u1-u11: sub-factors.

WAIS scales were innovative because, even if created for nonclinical purposes, they can be administered as clinical test batteries; they use the point scale concept instead of the age scale, so an IQ of 120 has a different meaning when you are in your 60s or in your 20s, but it has the same value in the group based on the age-range; they include a non-verbal performance scale, according with Wechsler's concept of intelligence, and able to partially overcame the biases caused by language. WAIS has been administered in different clinical populations, in order to see how the scores change, in which domains (i.e. verbal *vs.* performance) and how IQ performance differs from the general population. For example, the above

mentioned four-factor organization (**Figure 3**) was found to fit the data from a sample of 120 chronic schizophrenia and schizoaffective disorder outpatients, as well as it fitted the non-clinical comparison sample of 200 individuals drawn from the WAIS-III standardization sample; indeed it fitted the data from both samples better than alternative models (Dickinson, Iannone, & Gold, 2002).

Figure 3. WAIS-III and WAIS-IV Theoretical Scoring Measurement Model (Taub & Benson, 2013).



Legend: The 10 subtests, contributing to an individual's FSIQ are presented on the right side. These 10 subtests are then subsumed by one of the four first-order factors: Verbal Comprehension, Perceptual Organization, Working Memory and Processing Speed that are, in turn, subsumed by a general factor of intelligence or FSIQ.
This figure is taken for exemplificative purpose from: Taub & Benson (2013). Matters of Consequence: An Empirical Investigation of the WAIS-III and WAIS-IV and Implications for Addressing the Atkins Intelligence Criterion Historical Overview. *Journal of Forensic Psychology Practice*, 13, 27–48.
Abbreviations: *g*: general factor; uf1-uf4: first order factors; u1-u10: sub-factors corresponding to subtests.

Raw scores from each subtest (sometimes ameliorated with supplementary credit for timing performances) are converted in age-related scaled scores. These scores are used to derive the IQ that has a normal distribution with a mean of 100 and a standard deviation of ±3 that can be fitted into some ranges (See **Table 1**).

Table 1. IQ classification (Wechsler, 1997).

IQ Range	IQ Classification
130 and above	Very superior
120–129	Superior
110–119	High average
90–109	Average
80–89	Low average
70–79	Borderline
69 and below	Extremely low

Abbreviations: IQ: intellectual Quotient.

However, the full versions of the WAIS, often pose problems for many populations due to the length of administration (i.e. clinical populations or aged populations); furthermore, use of WAIS has been problematic in the research context. In fact, the complete test takes 80 min, on average, for healthy subjects (Wechsler, 1997), and close to 100 min in clinical samples (Ryan, Lopez, & Werth, 1998). A first four-test abbreviation of the WAIS (Wechsler, 1939) was made by Doppelt in 1956, by selecting two predictors of the total verbal score (Arithmetic and Vocabulary) and two predictors of the total performance score (Block Design and Picture Arrangement) (Doppelt, 1956). Ward's version (1990) estimated Verbal, Performance, and Full Scale IQs from seven subtests of the WAIS-R (Wechsler, 1981), and required about half of the administration time of the full test (Ward, 1990); this form has been revised by several authors. Wolfson and Bachelis (1960) first suggested a new methodology that has been broadly-used, based on the reduction of the items into each subtest, together with the subtest reduction (Wolfson & Bachelis, 1960). Since now, the development of short forms has been growing corresponding to the appearance of new versions of the full scale. A full revision of the shortened versions of the WAIS is reported in a recent review by Úbeda, Fuentes and Dasí (2016) that identified at least 5 short versions of WAIS published between 1953 and 1973, 12 shortened WAIS-R developed between 1982

and 1999, 6 shortened versions of the WAIS-III proposed between 1999 and 2010 and 3 short version of the WAIS-IV settled between 2013 and 2015 (Úbeda et al., 2016). In general, as the number of subtests increases, the predictive accuracy growths slightly so, the data indicate that is there not a perfect subtest combination for an abbreviated version, and that the best select-subtest combination may vary as a function of the type of subjects and of their efficiency to provide the information required (D. N. Allen et al., 1997; Guilmette, Dabrowski, Kennedy, & Gnys, 1999; Miller, Streiner, Goldberg, & Miller, 1996). For instance, in schizophrenia, the inclusion of an equal number of subtests from each factor could underestimate IQ, due to the deficits in working memory and processing speed (Blyler, Gold, Iannone, & Buchanan, 2000). So, Blyler and colleagues (2000) validated a short form of WAIS-III for schizophrenic patients, including one subtest from each of the four factors that was highly predictive of FSIQ for both schizophrenia patients and healthy controls, by comparing the validity of the four-factor short form with that of the best possible unrestricted four-subtest short form. Overall, the four-factor short form included Information, Blok Design, Arithmetic and Digit Symbol and was able to estimate IQ within five points for 70% of participants and within ten points for 94% of participants (both people with schizophrenia and controls). The extent of discrepancy between estimated and actual scores was unrelated to FSIQ level, so they possibly ruled out the potential flooring or ceiling effect that is often observed in several shortened versions of WAIS, especially when administered on psychiatric samples (Thompson, Howard, & Anderson, 1986).

5. Premorbid IQ

An estimate of premorbid intelligence is required when it is suspected that a patient has suffered cognitive decline, such as in brain injuries or in some psychiatric disease (i.e. schizophrenia). Clinicians often require information about pre-existing test results, academic records, employment history, or they can administrate tests that are assumed to be specific for measuring premorbid IQ.

Table 2 provides an overview of the most widely used methods to esteem premorbid IQ.

Table 2. Instruments for Assessing Premorbid IQ.

Type of test	Examples	Task	Strengths and limitations
Verbal sub-tests of the Wechsler Adult Intelligence Scale (WAIS), (Wechsler, 1997).	• Vocabulary • Information	To provide the definition of a list of increasingly difficult words. To answer a list of questions regarding general culture (i.e. in what continent is Argentina?). The total RS are converted in SS used to calculate the Full IQ.	They are considered less sensitive to the impact of age and various forms of brain damage. However, they are strongly affected by the integrity of long-term memory and might be unreliable in individuals with impaired memory.
Reading tests	• Wechsler Test for Adult Reading, WTAR (Holdnack, 2001). • National Adult Reading Test, NART (Nelson & Willison, 1991). • Wide Range Achievement Test (WRAT) (Wilkinson, 1993).	To read aloud a list of irregularly spelled words (whose transcriptions do not correspond to their pronunciation). The score obtained for each correct phonation is used to calculate the total RS, which is converted in a SS.	Since general spelling rules cannot be applied to irregular words, the correct pronunciation mainly relies on remote simple learning of vocabulary. However, they are not available for non-irregular languages.
Best estimate method	• (Lezak, 1983).	The highest test scores or the best performance in everyday tasks are the best estimate of the subject's premorbid ability, by using tests, other observations and historical data. This is the standard against which all other performance is measured.	A broad range of abilities are taken into account and not only a single battery of tests. Nonetheless, this test is not well linked to WAIS scores and tends to overestimate IQ scores.
Regression formulae	• (Barona, Reynolds, & Chastain, 1984) – USA sample. • (Crawford & Allan, 1997) –UK sample. • Oklahoma Premorbid Intelligence Estimations (OPIE) (Scott, Krull, Williamson, Adams, & Iverson, 1997).	Education, race, and occupation are the most powerful predictors of premorbid IQ. Occupation is the best predictor followed by age and years of education. This procedure combines both premorbid demographic variables of age, education, occupation, and race with current performance on the WAIS-R Vocabulary and Picture Completion subtests in estimating premorbid IQ.	Each variable assumes a value that can be used for a formula (e.g. sex-male=1; female=2 etc.). Demographic variables are easy to be obtained. However, the regression toward the mean artificially lowers or raises the estimated scores for cases falling outside one standard deviation of the population mean (i.e. above 120 or below 69).

Legend: the table provides a critical summary of the principal instruments used to assess premorbid IQ.
Abbreviation: RW: raw score; SS: Scaled Scores; IQ: intellectual quotient

Methods to estimate premorbid intelligence, traditionally rely on current performance levels believed to be resistant to deterioration, for instance starting from Cattel's theory of "Fluid and Crystallized Intelligences" (Horn & Cattell, 1966), several "hold tests" have been created. Subtests from WAIS – such as Information or Vocabulary – reading tests, i.e. the *Wechsler Test for Adult Reading* (Holdnack, 2001), the *National Adult Reading Test* (Nelson & Willison, 1991) or the *Wide Range Achievement Test* (Wilkinson, 1993). Other methods are based on inferring the best performance in everyday tasks, as the best estimate method (Lezak, 1983) or in regression formulae on demographic data (Barona et al., 1984; Crawford & Allan, 1997) and demographic variables and current performance (Scott et al., 1997). However, many of these methods demonstrate problems such as under- or overestimation of IQ and range restrictions (Mortensen, Gade, & Reinisch, 1991) so they are not reliable for the purpose of assessing people who develop psychosis, who are generally on the low average range for IQ. Therefore, the most accurate strategy is using different premorbid IQ estimates depending upon the estimated range of intelligence of the individual being assessed (Griffin, Mindt, Rankin, Ritchie, & Scott, 2002).

5.1. Psychosis, Cognition and Premorbid Adjustment

Premorbid adjustment in psychosis is defined as the ability of a person to make social and intimate relationships as well as the academic achievements before the onset of psychotic symptoms and is related to the onset and the prognosis of the illness (Addington & Addington, 2005; Bailer, Bräuer, & Rey, 1996; Torgalsbøen, 1999).

In schizophrenic patients, an impairment of premorbid adjustment involving several areas of functioning has been broadly reported, especially disturbances in interpersonal relations, withdrawal from normal social interactions and poor relationships with peers (Cannon et al., 2001; Hans, Marcus, Henson, Auerbach, & Mirsky, 1992). When present in childhood, the impairment has been suggested to be variable in its age of onset and course over time, degree of severity, functional

domains involved and specificity (Cannon et al., 2001; Neumann, Grimes, Walker, & Baum, 1995).

Furthermore, women generally report significantly better premorbid functioning than men (Foerster, Lewis, Owen, & Murray, 1991; Torgalsbøen, 1999) and they have different neurodevelopmental trajectories in social and academic domains (D. N. Allen et al., 2013).

Nonetheless, premorbid impairment is not present in all patients, since a proportion of them (frequently those with an abrupt onset) have a relatively good premorbid functioning (McGlashan, 2008; Neumann et al., 1995).

It has been reported that premorbid social and academic function constitute fairly independent dimensions (D. N. Allen, Kelley, Miyatake, Gurklis, & van Kammen, 2001; Barajas et al., 2013; Larsen et al., 2004).

A better premorbid social adjustment is an important aspect in functional outcome (Ayesa-Arriola et al., 2013) and it is related with an earlier age of onset (Cannon-Spoor, Potkin, & Wyatt, 1982; Goldberg et al., 2011; Larsen et al., 2004). While good premorbid adjustment appears to be associated with an acute onset of the illness, poor premorbid adjustment is more often related to an insidious onset (Bailer et al., 1996). In fact, impaired premorbid functioning is associated with a higher severity of negative symptoms and poorer post-morbid social functioning (Ayesa-Arriola et al., 2013; Chang et al., 2013; Galderisi et al., 2013; Rabinowitz, De Smedt, Harvey, & Davidson, 2002).

Moreover, schizoaffective disorder was found to be associated with better premorbid adjustment than schizophrenia in the academic domain, but not in the social domain, that remains the most impaired function across all the schizophrenic-related disorders; whilst mood disorders with psychotic features have better premorbid adjustment than schizoaffective and schizophrenic disorders (Norman, Malla, Manchanda, & Townsend, 2005; Saracco-Alvarez, Rodríguez-Verdugo, García-Anaya, & Fresán, 2009; Tarbox, Brown, & Haas, 2012).

A possible explanation is that, while in schizophrenia spectrum patients a better cognitive performance is predictive of higher psychosocial functioning, depressive symptomatology is a stronger predictor of psychosocial functioning than cognition,

in bipolar patients; that seems to reflect the fact that the impact on daily life is present in schizophrenia to a greater extent than in bipolar disorder (Jabben, Arts, Van Os, & Krabbendam, 2010).

Premorbid functioning –especially premorbid academic adjustment– is related to premorbid IQ (Barajas et al., 2013; Norman et al., 2005) and both directly predict post-morbid IQ and negative symptoms, and indirectly predict post-morbid social and occupational functioning, through negative symptoms (Brill et al., 2009).

Other evidence in this direction suggests that better social and occupational outcomes, along with more education and more meaningful activities, occur in patients with few negative symptoms, better working memory and higher childhood academic functioning (Larsen et al., 2004).

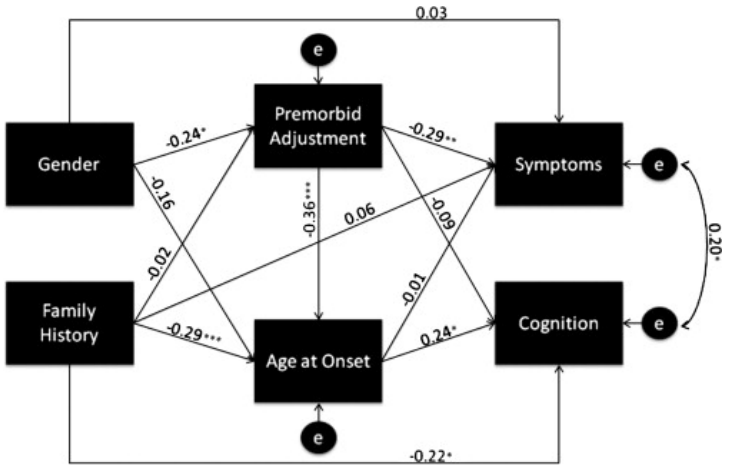
It has been suggested that premorbid academic impairment could be related to the genetic risk for schizophrenia, as poor academic functioning has been observed among unaffected siblings of people with familial schizophrenia, compared with healthy controls (Walshe et al., 2007).

It has been proposed that the supposed entity of "Deficit Schizophrenia" or "Negative Syndrome" as opposed to "Non-Deficit Schizophrenia", is related to male gender (Roy, Maziade, Labbé, & Mérette, 2001), increased presence of familial history of psychosis (Kirkpatrick, Ross, Walsh, Karkowski, & Kendler, 2000) and poor premorbid adjustment –especially in the social domain (Strauss et al., 2012) – as well as more severe clinical outcome in terms of cognition and symptomatology (Bucci et al., 2015; Carpenter, Heinrichs, & Wagman, 1988; Fenton & McGlashan, 1994; Malaspina et al., 2000).

In this model, age at onset and premorbid functioning are proposed as mediators between gender, familial history of psychosis and clinical outcome (Bucci et al., 2015), in accordance with the notion that the "deficit" entity has a different developmental trajectory, and that premorbid adjustment is one of the essential aspects of its characterization (Galderisi & Maj, 2009; Goldberg et al., 2011).

Figure 4 describes all the theoretically-driven associations between markers of liability to schizophrenia, into the model of the Deficit Syndrome (Goldberg et al., 2011).

Figure 4. The Model of Deficit Syndrome and the Associations Between Markers of Liability to Schizophrenia (Goldberg et al., 2011).



Legend: this model includes all theoretically-driven associations between markers of liability to schizophrenia. Lack of statistical significance of some of the explored effects suggests that the model may be overcomplicated. Standardised regression weights for the direct effects are shown. *=p<0.05. **=p<0.01. ***=p<0.001

Despite the plausibility of this model, it has not been demonstrated that deficit schizophrenia is a discrete entity rather than the end of a distribution.

5.1.1. Psychosis and Cognition: life-long disease?

Cognitive abnormalities have been noted since Emil Kraepelin named what later became schizophrenia as *dementia praecox* and commented «The patients are distracted, inattentive... they cannot keep the thought in mind» (Kraepelin E, 1919). However, it was long thought that the deficits displayed on formal psychologic testing were due to impaired motivation or cooperation or to the symptoms (Brody, 1941).

At present, it is well recognized that intellectual impairment is a common feature of schizophrenia (Bora et al., 2010; Matheson, Shepherd, Laurens, & Carr, 2011; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; Zanelli et al., 2010) that also occurs, though to a lesser extent, in affective psychosis (Bora, Yucel, & Pantelis, 2009; Krabbendam, Arts, van Os, & Aleman, 2005; Kravariti et al., 2009). The average cognitive impairment in schizophrenia can reach two standard deviations below the healthy controls' mean (Heinrichs & Zakzanis, 1998); patients

generally perform more poorly than would be expected based on their parent's education level (Keefe, Eesley, & Poe, 2005), their unaffected monozygotic twins (Goldberg et al., 1990) and their premorbid level (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009).

However, two different meta-analyses have found that children who later develop schizophrenia are generally 0.4–0.5 standard deviations below the population average on IQ (Khandaker, Barnett, White, & Jones, 2011; Woodberry, Giuliano, & Seidman, 2008).

Cognitive deficits are present at the time of the first episode (Harvey & Bowie, 2003) and there was a long debate about the possibility that these deficits progress before or after the onset or whether they stay stable during the course of the illness; i.e. a debate regarding the neurodevelopmental (Murray & Lewis, 1987; Murray, O'Callaghan, Castle, & Lewis, 1992) or neurodegenerative (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006) trajectory of cognitive deficits in schizophrenia.

First studies suggested the occurrence of a light-to-mild general intellectual decline in schizophrenia, within the first five years (Johnstone, Leary, Frith, & Owens, 1991; Nelson et al., 1990; Waddington & Youssef, 1996; Waddington, Youssef, & Kinsella, 1990) but they generally considered chronically institutionalized patients.

More recent studies have made an effort to consider differences between people at risk for psychosis, first episode psychotic patients and the subgroup of them that came into the strictest diagnosis of schizophrenia.

Some cross-sectional studies indicate a cognitive decline over the onset, followed by a selective drop in some domains, i.e. shift attentional set (Pantelis et al., 2009), within the first years after the onset and present in patients with established schizophrenia. A meta-analysis also suggests a larger IQ impairment in the first episode psychotic patients compared to the premorbid period, but comparable to later phases of illness and followed by a deficit stability (Mesholam-Gately et al., 2009). In contrast, other studies have demonstrate that, following psychosis onset, the IQ of patients stays stable (Leeson, Sharma, et al., 2011). Also

the two abovementioned meta-analyses on premorbid IQ, did not evidence a greater IQ deficit with advancing age (Khandaker et al., 2011; Woodberry et al., 2008).

A recent meta-analysis by Bora and Murray (2014) on 25 studies compared people at risk for psychosis, first episode psychotic patients followed up within the first five years and healthy controls. The study has shown that there is no evidence of a cognitive deterioration, and there are no differences in global cognition and single domains improvement between these three groups (Bora & Murray, 2014), thus contradicting the theory of a deterioration in psychotic patients (Hedman, van Haren, van Baal, Kahn, & Hulshoff Pol, 2013) and sustaining the neurodevelopmental origin of a life-long and stable cognitive impairment.

5.1.2. Psychosis and Cognition: General vs. Specific

5.1.2.1. Domains vs. General Factor

Some separable cognitive factors have been presented as fundamental dimensions of cognitive deficit in schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, verbal comprehension and social cognition (Nuechterlein et al., 2004).

Memory and verbal memory are generally impaired in first episode patients regardless of IQ (O'Connor et al., 2012). It has been suggested that impairment in verbal learning and memory shares a genetic overlap with schizophrenia, is a valid endophenotype for the condition (Owens et al., 2011), and it is associated with an earlier disease onset (Tuulio-Henriksson, Partonen, Suvisaari, Haukka, & Lönnqvist, 2004). The specific domain of working memory has been suggested as a core component in schizophrenia cognitive deficit (Silver, Feldman, Bilker, & Gur, 2003), as it is related to prefrontal cortical regions (Callicott et al., 1999) such as processing speed. This latter component accounts for most of the differences in cognition between patients with schizophrenia and healthy controls and might be mediating impairments of working memory, executive functioning, and other cognitive disturbances (Ojeda et al., 2012; Rodríguez-Sánchez, Crespo-Facorro,

González-Blanch, Pérez-Iglesias, & Vázquez-Barquero, 2007). A recent meta-analysis on 40 studies (1,961 patients and 1,444 controls) confirmed that processing speed measures discriminate people with schizophrenia from comparison individuals better than more widely studied neuropsychological instruments (Dickinson, 2008; Dickinson, Ramsey, & Gold, 2007).

Nevertheless, some authors have noticed that cognitive ability, as reflected in test performance, appears to be more unitary in schizophrenia than in healthy subjects (Dickinson, Ragland, Calkins, Gold, & Gur, 2006) so they refer to a "*g*" common cognitive ability factor that appear to be largely impaired in schizophrenia (Dickinson & Gold, 2008; Dickinson, Iannone, Wilk, & Gold, 2004; Dickinson, Ragland, Gold, & Gur, 2008).

General impairment has been proposed as associated with reduced grey matter, diminished myelin density and inflammation, oxidative stress, poor signal integration and abnormalities associated with glutamate (Dickinson, 2008). But this deficit could also be related to other factors such as substance misuse and the effects of prescribed medications (Zipursky, Reilly, & Murray, 2013).

Moreover, to be involved in a less challenging social world could play a role, thus decreasing stimuli in a two-way relationship with cognitive functions. In fact, impairments in vigilance and verbal memory are related to social deficits, lower community functioning and skill acquisition, probably through a difficulty in following simple activities such as social conversations, instructions and reading (M. F. Green, 1996; M. F. Green, Kern, Braff, & Mint, 2000). Speed processing, and working memory impairment are associated with employment status (Gold, Goldberg, McNary, Dixon, & Lehman, 2002; McGurk & Meltzer, 2000) and a generalized impairment in multiple domains is related to an amount of daily life activities (Evans et al., 2003).

5.1.2.2. All Patients vs. Subgroups of Patients

However, not all psychotic patients show cognitive impairment (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000). From an epidemiological study of first-admission psychotic patients, we know that as many as 16% of schizophrenic,

20% schizoaffective, 42% of bipolar, and 42% of depressed patients may not be cognitively impaired (Reichenberg et al., 2009). Furthermore, there are some patients meeting diagnostic criteria for schizophrenia who have markedly superior premorbid intellectual and actual level and appear indistinguishable from IQ-matched healthy controls; these subjects appear be free of gross neuropsychological deficits (MacCabe et al., 2012).

So questions remain about the amount of premorbid IQ deficit, whether this is due to a decrement in the majority of future cases (a left-shift of this population), or whether it is due to a minority effect driven by a sub-group with conspicuously low IQ (Khandaker et al., 2011).

5.1.2.3. Continuum vs. Categorical Disorders

Although neurocognitive deficits are evident both in schizophrenia and bipolar disorder, two longitudinal studies have suggested that neurodevelopmental abnormalities are present in schizophrenia but not in bipolar disorders, and that individuals with better cognitive functioning in childhood or adolescence have an increased risk for later bipolar disorders (Koenen et al., 2009; MacCabe et al., 2010).

A recent meta-analysis by Trotta, Murray and McCabe (2014) has revealed that the severity of cognitive deficits and its consequences appear to partly differ between schizophrenia and bipolar disorder. Although impairment on overall intellectual functioning is present in both schizophrenia and bipolar patients, schizophrenia, not only shows significant deficits in premorbid cognitive function, but also is characterized by severe post-onset impairment. Bipolar disorders, show a much smaller premorbid deficit, that becomes null when the analysis is restricted to prospective studies, and suffer a greater degree of post-onset impairment, though ultimate impairment remaining much smaller than that found in schizophrenia (Trotta, Murray, & MacCabe, 2015). It has been proposed that, on a background of shared genetic predisposition to psychosis, schizophrenia, but not bipolar disorder, is subject to additional genes or early insults, which impair neurodevelopment, that make the difference between these two diseases (Murray et al., 2004).

Other clinical entities that lie in an intermediate position between the schizophrenia–bipolar disorder continuum are affective psychoses (psychotic depression, psychotic bipolar disorder/mania) and schizoaffective disorders (American Psychiatric Association, 2013). A meta-analysis by Bora, Yucel and Pantelis (2009) has suggested that diagnoses in the schizoaffective disorder and affective psychosis group only slightly affect the degree of cognitive impairment in these groups relative to schizophrenia (Bora et al., 2009).

Bipolar disorder has been proposed as an intermediate phenotype between schizophrenia and healthy controls (Bora & Pantelis, 2015), in a common genetic vulnerability in which more prominent affective features and less enduring psychosis are associated with less cognitive impairment, thus including in the continuum affective psychoses and schizoaffective disorders (Hill et al., 2013; Hill, Harris, Herbener, Pavuluri, & Sweeney, 2008).

6. Cannabis

Cannabis embodies the 38% of the European illicit-drug market that supplies over 22 million annual users by constituting the largest drug market in Europe (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016). Despite its large impact on the community, little is known on this substance and its potential harmful effects.

Talking with people from my community and with patients suffering of several diseases, I had the impression that most young people believe that laws on cannabis are too restrictive, in light of its relatively innocuous consequences on people and it is not infrequent to see articles in newspapers on this issue (e.g. Turrini, 2015). In Italy there is now an association that is nowadays collecting firms for claiming rights on therapeutic use of cannabis and legalization (Associazione Cannabis Terapeutica; ACT, 2001). Other people simply disagree with the idea of its legalization, for moral reasons (e.g. Ricciardi, 2014). Someone else hopes for medical benefits, or affirms that its even illegal-use is a self-cure approach against

social inhibition, stress, insomnia, rumination or psychological pain and for positive affect enhancement (B. Green, Kavanagh, & Young, 2004).

Even if several studies have demonstrated a relationship between social anxiety and cannabis problems (Buckner & Zvolensky, 2014; Foster, Ecker, Zvolensky, & Buckner, 2015; Foster, Garey, Buckner, & Zvolensky, 2016), other studies suggested a protective function of symptoms of social anxiety for cannabis in adolescents from the general population, probably through a less peer involvement (suggesting increased social isolation) for those adolescents with higher levels of symptoms of social anxiety (Nelemans et al., 2016; Schmits, Mathys, & Quertemont, 2015). So, the precise relationship between cannabis use and anxiety has yet to be established (Crippa et al., 2009).

While the psychological involvement with cannabis will be one of the points of interest of this thesis, the controversial legal issue about cannabis is no-longer debated in this context, but it suggests that it's difficult to identify an "overall" dangerous effect of this substance, because it depends on the users and the pattern of use and the type of cannabis used. In fact, although for many people cannabis use is experimental and short-lived, for a minority its use can become problematic and have serious long-term consequences (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

The *National Survey on Drug Use and Health* has estimates that 5.4 million use marijuana on a daily basis (Substance Abuse and Mental Health Services Administration, 2014); daily users in the European Union (EU) are estimated at 3 million (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016). Approximately 83.2 million of 15 to 64-year-olds adults in the EU, are estimated to have tried this drug at least once in their lifetime. Use is higher among young adults (aged 15-34 years), with almost 16.6 million individuals, having used cannabis in the last year (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

In some high-consuming countries (i.e. UK), trends in prevalence of use have been showing marked declines, but other countries show intensification; in fact, EU has seen an increasing number of people seeking treatment for cannabis-related

problems overall (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

Cannabis is a naturally occurring plant with psychotropic properties that can be cultivated out- and indoors, and marijuana is produced by drying the flowering tops of the plants. Hashish is the other most common form of cannabis product, deriving from plant resin and generally compacted into blocks. While the latter is largely mass-produced for export, mostly in Morocco, the former is increasingly grown for domestic markets: it is less likely to be intercepted by authorities, it increasingly dominates the market in EU and it can be rendered of high potency by indoor techniques (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016), in order to respond to market requests.

The main psychoactive component, tetrahydrocannabinol (Δ-9-THC) has increased in commercially herbal products in the past 50 years from 1% up to 15% (Levounis & Herron, 2014) in products called “skunk” and “super-skunk”, from their strong smell. This constituent is responsible for the positive psychoactive effect of the drug, and it is potentially able to produce tolerance and desensitization.

The other main constituent of cannabis is cannabidiol (CBD), which has anxiolytic and antipsychotic properties, and seems to “balance” the psychotogenic effect of THC (S. Bhattacharyya et al., 2010; Di Forti et al., 2009). Consequently, any reduction of CBD in illicit cannabis (such as in “skunk” variety) can have implications for the overall negative health consequences associated with consumption (European Monitoring Centre for Drugs and Drug Addiction and Europol, 2016).

The endogenous cannabinoid system is involved in mood and appetite regulation, immunity-system, pain management and memory; however, the exact subtle elements of how cannabis influences them are still broadly obscure (Grant & Cahn, 2005).

6.1. Cannabis and Intellectual Quotient (IQ)

The association between cannabis use and cognitive performance has been widely studied. The following paragraphs are a revision of a previously published-review on this topic (Ferraro, Sideli, & La Barbera, 2017-*in press*).

Table 3 shows a non-exhaustive summary of the principal reviews on this subject with authors' conclusions.

In 1995, Pope and colleagues (H. Pope, Gruber, & Yurgelun-Todd, 1995) first tried to distinguish between the acute and residual effects of cannabis in individuals without any psychiatric disorders. They revealed a residual effect on attention, psychomotor tasks, and short-term memory during the 12-24 hours-period immediately after cannabis use, among naturalistic and controlled studies. They also considered long-term effects as these lasting after 24 hours of abstinence, but they revealed insufficient evidence to support or refuse a more prolonged drug residue effect, after this period (H. Pope et al., 1995); so the authors argued that, in future studies, it would be very important trying to exclude the virtual continuous effect of acute intoxication and the confounding effect of withdrawal syndrome, that could have been responsible for the effect detected during the first 24 hours.

With this consideration in mind, they later tried to define the neurotoxicity of cannabis as its long-term residual effect lasting after 28 days of abstinence and tested people who had used cannabis on an almost daily basis (H. Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2002, 2001; H. Pope, Gruber, & Yurgelun-Todd, 2001). Their results suggested deficits in memory and attention present for days after discontinuing use but mainly reversible after four-five weeks (H. Pope, Gruber, & Yurgelun-Todd, 2001), regardless of the cumulative amount of lifetime cannabis use (H. Pope et al., 2002).

Gonzalez and colleagues (2002) examined the methodology adopted in the previous literature on the basis of the correspondence to *a priori* criteria (see **Figure 5**) in order to ensure that between-group (case/control) differences could be attributable to differences in history of cannabis use, without any effect of potential confounders.

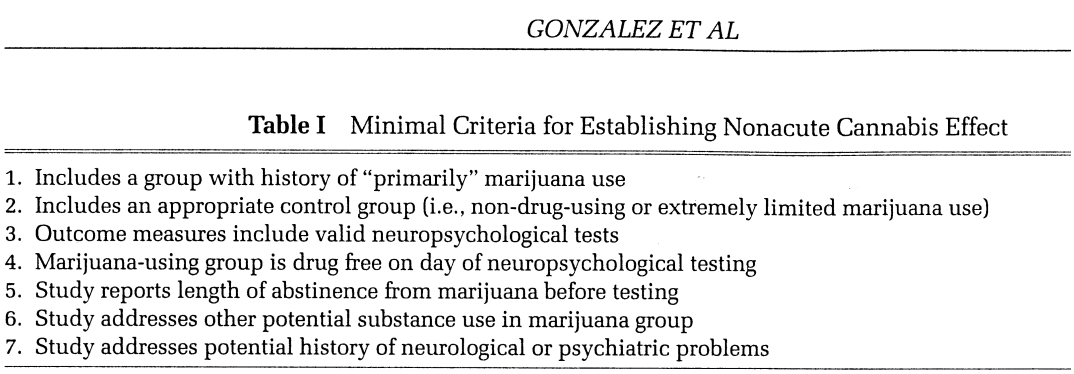
Table 3. Reviews and Meta-analysis on Cannabis and Cognition.

Authors	Study type	Number of studies included (years of publication)	Cannabis effect targeted	Impaired domains
Pope et al., 1995	Review	42 (1972-1993).	RE =12-24 HA. LTE >24 HA.	RE: attention, psychomotor tasks, short-term memory. LTE: minimal.
Pope, Gruber, Hudson, et al., 2001	Review	8 (1996-2001) RE. 7 (1989-2000) LTE.	RE <28 DA. LTE >28 DA.	RE: memory and selective attention. LTE: minimal.
Gonzalez, Carey, & Grant, 2002	Review	40 (1973-2002).	RE >24 HA.	RE: attention and working memory.
Grant et al., 2003	Meta-analysis	11 (1977- 2002).	RE >24HA.	RE: global performance, learning and forgetting.
Gonzalez, 2007	Review	20 (1980-2007) AE. 19 (1999-2006) RE.	AE ≤12 HA. RE >24 HA.	AE: memory retrieval. RE: memory.
Jacobus, Bava, Cohen-Zion, Mahmood, & Tapert, 2009	Review	16 (1989-2008).	RE <28 DA. LTE >90 DA.	RE: attention, processing speed, verbal learning and memory. LTE: none.
Solowij & Pesa, 2010	Review	116 (2000-2010).	AE ≤24 HA RE =24 HA - 28 DA.	AE and RE: attention, inhibition, verbal memory and other memory processes.
Crean, Crane, & Mason, 2011	Review	12 (1970-2009) AE; 14 (1995-2010) RE; 11 (1995-2006) LTE.	AE ≤6 HA. RE =7-20 DA. LTE >21 DA.	AE: working memory, attention and inhibition. RE: decision making and risk taking. LTE: none.
Schreiner & Dunn, 2012	Meta-analysis	33 (2000-2011) RE; 13 of them on LTE.	RE >4 HA. LTE >25 DA.	RE: global performance, most cognitive domains. LTE: none.
Crane, Schuster, Fusar-Poli, & Gonzalez, 2013	Review	34 (2007-2012) AE; 61 (2007-2012) RE.	AE <8 HA RE >8 HA.	AE: learning and memory, attention, concentration and working memory. RE: episodic memory, attention, concentration, risk taking and decision making.

Legend: the table presents a summary of the principal reviews about cannabis use and acute, residual and long-term effects on cognition with authors' findings.
Abbreviations: AE: Acute Effect; RE: residual Effect; LTE: Long-Term Effect; HA: Hours of Abstinence; DA: days of abstinence. Ferraro et al. (*in press*).

Their results were consistent with those from Pope and colleagues. Twenty-two of the 40 studies included in their review, reported at least some subtle impairments (mainly in attention and working memory) after 24 hours of abstinence. Despite methodological rigor authors indicated, as a limitation, that very few studies, among those considered, assessed premorbid neuropsychological abilities and they, usually, looked at vocabulary or verbal fluency tests.

Figure 5. A priori Criteria Established from Gonzalez et al. (2002) in Studying Non-acute Cannabis Effect.



GONZALEZ ET AL

Table I Minimal Criteria for Establishing Nonacute Cannabis Effect

1. Includes a group with history of "primarily" marijuana use
2. Includes an appropriate control group (i.e., non-drug-using or extremely limited marijuana use)
3. Outcome measures include valid neuropsychological tests
4. Marijuana-using group is drug free on day of neuropsychological testing
5. Study reports length of abstinence from marijuana before testing
6. Study addresses other potential substance use in marijuana group
7. Study addresses potential history of neurological or psychiatric problems

Legend: this table is taken for exemplificative purpose from Gonzalez, R., Carey, C. & Grant, I. (2002). Nonacute (residual) neuropsychological effects of cannabis use: a qualitative analysis and systematic review. *J Clin Pharmacol*, 42, 48S-57S.

The same group performed a meta-analysis in 2003 (Grant et al., 2003). The average global neurocognitive effect was small and was expressly observed in memory and forgetting/retrieval tests, but very few studies on the non-acute neurocognitive effects of cannabis meet current research standards. A small effect was also been observed by Gonzalez (2007) in frequent and heavy cannabis users, and this was not necessarily matched with changes in brain functioning. Authors conclude that heavy cannabis use may produce some deficits, but it has not been determined if such deficits are a result of cannabis use or if they represent premorbid problems that may have contributed to the development of a cannabis use disorder (Gonzalez, 2007).

All the same, results from Gonzalez and Grant's group appear not to be able to resolve the question about long-term neurotoxicity, given that most of the cannabis users included in their studies had been abstinent for a maximum of two weeks. In fact, in a recent update of Grant's work published by Schreiner and Dunn (2012), most of the cognitive domains assessed as well as the overall performance remained impaired when subjects were tested within the first 25 days of abstinence but not after this period. So, the clinical significance of these findings remained unclear due to the possible effect of the withdrawal syndrome. To sum up, this study including two different meta-analyses, indicated a small negative residual effect and no

lasting effects on neuropsychological performance, regardless of the duration of use (Schreiner & Dunn, 2012).

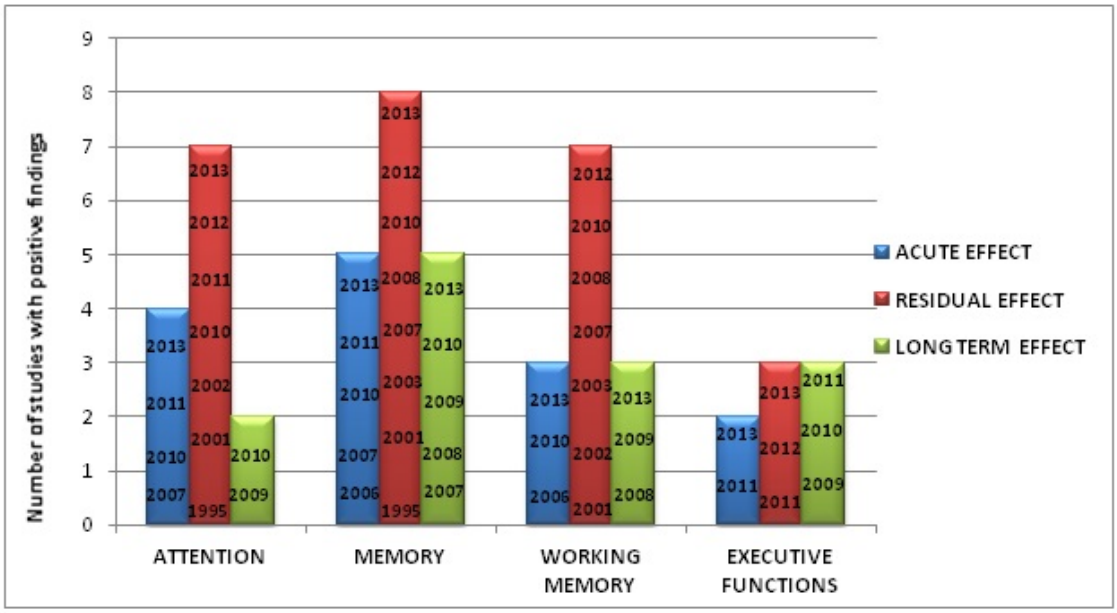
Besides the amount of cannabis used and abstinence length, another crucial point when considering the harmful effects of cannabis on cognition, is the age of first cannabis use. Jacobus and colleagues (2009) addressed this point in a review and concluded that adolescents who use marijuana heavily tend to show disadvantages in attention, processing speed, verbal learning and memory that persist beyond one month of abstinence, but largely remit after three months of sustained abstinence. Once again, without any measure of premorbid IQ, it is difficult to establish whether a causal direction exists between cannabis use and cognition.

Di Forti, Morrison, Butt, & Murray (2007) addressed "the chicken or the egg" question by claiming the role of an earlier age of onset in using cannabis as determinant in the detrimental effect of the substance on cognition and hypothesizing a gene-environment pattern of common vulnerability to cannabis effect and psychosis, where neuropsychological deficits underlay a profile of people at-risk to develop psychosis without the need for the additional risk factor of cannabis use. This is of particular interest in this context and is going to be subsequently taken into account.

Other executive functions have received more attention in recent years (Crane et al., 2013; Crean et al., 2011). For example, residual effects of cannabis on risk taking and decision making were found to be impaired in two reviews, especially when studies take into account the distinction between chronic, heavy cannabis users, as opposed to light and occasional users (Crean et al., 2011) and the necessity to take into account the role of gender in producing such as impact, as it has been less studied (Crane et al., 2013). However, these studies are far from clarifying the temporal ordering of cognitive deficits and cannabis use. As is shown in **Figure 6**, most of the reviews concentrate on residual and long-term effects. Residual effects are the most-represented findings over the years, especially in the memory domain, and positive results on long-term effects of cannabis probably depend on ameliorated research designs. Very few papers from those mentioned above considered general IQ as a measure of interest; those that did, largely found a small

residual effect on overall impairment but not after a long-term period of abstinence (Grant et al., 2003; Schreiner & Dunn, 2012).

Figure 6. Cannabis use and cognitive functioning.



Legend: this histogram provides an overview of the main findings on cannabis use and cognition mentioned in this chapter. Cognitive functions are on the X-axis, and the number of studies with positive findings on deterioration for each domain, divided according to acute effect (in blue), residual effect (in red), and long-term effect (in green), are counted on the Y-axis. Each bar cumulates studies on the field indicated, by referring to their year of publication – from the holder to the newest – Ferraro et al. (*in press*).

Other reviews have restricted their interests to memory (data not shown in table), by ascertaining an impairment in this domain during the acute phase (Ranganathan & D'Souza, 2006) and in the long-term (Solowij & Battisti, 2008) together with attention and inhibition, depending on duration, frequency, dose and onset of cannabis use in adolescence (Solowij & Pesa, 2010).

Ranganathan and D'Souza (2006) controlled dose, route of administration, sample sizes and sample selection effects, other drug use, tolerance and dependence to cannabinoids, and the timing and sensitivity of psychological tests towards 35 studies conducted between 1970 and 2006. They concluded that acute administration of Δ-9-THC transiently impairs immediate and delayed free recall of information presented after, but not before, drug administration in a dose- and delay-dependent manner, particularly with the inhaled and intravenous route.

Schoeler & Bhattacharyya, 2013 have recently highlighted the role of the mix of different cannabinoids present in the type of cannabis used in studies on cognition; this is another point of important concern, as the components of street-cannabis have been changing in the last years. In the long-term, impairments in memory seem particularly likely to persist following abstinence if regular and heavy use of cannabis high in Δ-9-THC is started at an early age (Schoeler & Bhattacharyya, 2013). These data are consistent with those from a recent review (Lorenzetti, Solowij, & Yücel, 2016) on 31 studies of neuro-anatomic alterations related to cannabis use, which are mostly present in regions that are highest in cannabinoid receptors, such as prefrontal cortex, hippocampus, amygdala and cerebellum and that are associated with greater dose and earlier age of onset. Authors highlight that preliminary evidence shows that THC exacerbates, whereas CBD protects from, such harmful effects (Lorenzetti et al., 2016).

The best way to address this issue would be a longitudinal study, able to measure cognitive performance before and after the period of life in which cannabis is consumed. On the other hand, although the problem of possible confounding and the difficult to control the street-drug components, some principal authors on this topic claim that naturalistic and retrospective studies of drug users remain the most efficient way to assess the long-term cognitive effects of cannabis consumption. Prospective designs are extremely expensive, time-consuming and, in some cases, unethical (H. G. Pope, 2002; Solowij, Stephens, Roffman, & Babor, 2002).

In the next section we will review the existing longitudinal studies on premorbid IQ in cannabis users, along with measures of premorbid IQ assessed in the aforementioned papers.

6.2. Cannabis and Premorbid-IQ

Pope and colleagues estimated premorbid IQ by using a vocabulary test which resulted in lower scores among heavy users than controls, additionally attenuating differences in cognitive performance between the two groups when entered as covariates (H. Pope, Gruber, Hudson, et al., 2001). Solowij and Battisti (2008)

reported three studies showing lower vocabulary scores in cannabis users compared to controls. Schreiner and Dunn (2012) indicated a similar impairment on overall performance in the verbal/language domain – assessed by vocabulary, verbal fluency and naming tests – within the first 25 days of abstinence, but surprisingly not after this period of time.

Taken together, these results suggest, as already mentioned, that vocabulary and – not surprisingly – verbal fluency tests, behave more as measures of actual capacities than as an estimation of premorbid IQ. In retrospective studies, reading tests have been suggested as a better method, because they are able to provide a broad estimate of general ability before eventual impairment as opposed to other tests (Griffin et al., 2002).

Table 4 provides a resume of longitudinal studies that specifically assessed IQ before and after cannabis use. In the early 80's Kellam, Ensminger & Simon (1980) tested a large cohort of Afro-American adolescents from Woodlawn, an urban, poor community on the South Side of Chicago, at their first degree school and re-tested them ten years later, revealing that people with higher IQ, better social adaptive capacities and readiness-for-school higher scores were more likely to use cannabis in their teenage years. Fleming Kellam & Brown (1982) later showed on the same population that boys with higher IQ and readiness-for-school tended to initiate substance use at an earlier age and girls who were rated as shy or having learning problems, tended to initiate use at a later age. Ensminger, Juon & Fothergill (2002) re-interviewed 952 subjects from this original cohort at age 32 and confirmed that males having superior IQ scores in childhood were more likely to initiate cannabis use in adolescence but were also more likely to discontinue this behavior as young adults, while to be shy or aggressive was a risk factor for becoming a persistent cannabis user as an adult.

Fried and colleagues (2002, 2005) had the opportunity to follow-up a group of young subjects as part of *The Ottawa Prenatal Prospective Study*, and assessed their IQ before, during and after cessation of regular marijuana use. Young adults with heavy actual or former use, started with a lower IQ compared to non-users (who had never used cannabis regularly, i.e. once a week) and who had not used any cannabis

in the past 2 weeks) and light users (less than 5 joints per week, at least once a week); but only heavy use (at least 5 joints per week) was related to a lower IQ when compared to the other groups. However, similar deficits were no longer apparent 3 months after cessation of regular use (Fried, Watkinson, & Gray, 2005; Fried, Watkinson, James, & Gray, 2002).

Different findings were derived from two different British cohort studies by White and colleagues (White & Batty, 2012; White, Gale, & Batty, 2012). They found that a higher childhood IQ may increase the risk of illegal drug use – e.g. "cannabis lifetime" – in adolescence and adulthood, even when correcting for material disadvantage, antisocial behavior, social distress and anxiety. However, the same group (White, Mortensen, & Batty, 2012) found an apparently contrasting result on a group of males US Vietnam veterans with IQ assessed at the time of the military service enrollment. That is, subjects with higher IQ scores were less likely to be habitual users of cannabis, during active service (i.e. for once a week, ≥3 months) and in civilian life (in the past 12 months, ≥once a week), with a moderating effect of socioeconomic status in adulthood.

Meier and colleagues (2012) published a paper where people from the Dunedin Cohort Study were followed-up from childhood to the age of 38. Subjects with more persistent cannabis dependence (that had generally started in adolescence) presented greater IQ decline, not specific to any domains, when compared to study members who never used cannabis. Persistence of regular cannabis use was defined as the total number of study waves out of five at which a study member reported using cannabis four days a week or more (the majority of days in a week) (Meier et al., 2012). Study members who never used cannabis, experienced a slight increase in IQ. Results stayed significant after ruling out possible confounders such as education, diagnosis of schizophrenia, tobacco and other-drug dependence and past-week cannabis consumption. Interestingly, people who reported a lifetime recreational use of cannabis, but not dependence, started with a higher IQ than people that never used cannabis. These two groups had similar IQ levels at age 38.

Table 4. Longitudinal Studies on Premorbid IQ and Cannabis Use.

Authors	Study	Sample size	Pattern of cannabis use as described by authors	Measures (age in years of the valuation)	Conclusions
Kellam, Ensminger & Simon, 1980	1966-1967 first graders Woodlawn African Americans –USA.	705	Lifetime	IQ (6; 16)	Higher IQ, social adaptive capacities and readiness-for-school scores in childhood predict cannabis use in teenage years.
Fleming, Kellam, & Brown, 1982					Subjects with higher IQ and readiness-for-school in childhood tend to initiate cannabis use at an earlier age. Shy girls or girls with learning problems tend to start use later.
Ensminger et al., 2002		952	Discontinue; Persistent	IQ (6; 32)	Males having higher IQ in childhood are more likely to initiate in adolescence but also to discontinue use as young adults. Low-scoring females are less predisposed to a persistent use.
Fried, et al., 2002	Ottawa Prenatal Prospective Study (OPPS) – Canada.	70	Light current regular;	IQ (12; 17-20)	Overall IQ and other domains impaired in heavy current users but for no longer than 3 months after cessation of regular use.
Fried, Watkinson & Gray, 2005		113	Heavy current regular; Former regular; None.	IQ, processing speed, memory, vocabulary attention, abstracting abilities. (12; 17-20)	
White & Batty, 2012	1970 British Cohort Study – UK.	7,946	Lifetime	IQ (5; 10)	High childhood IQ increases the risk of use in adolescence and adulthood, especially in women.
White, Gale, & Batty, 2012	1958 National Child Development Survey – UK.	6,713	Lifetime	IQ (11; 42)	Use in middle age is more probable in children with a greater IQ, especially woman.
White, Mortensen, & Batty, 2012	Vietnam Experience Study – USA.	14,362	Habitual	IQ (22; 40)	Subjects with higher IQ at 22 are less likely to be habitual users, during active service and in civilian life. This association is attenuated by confounding variables.
Meier et al., 2012	Dunedin Cohort Study – New Zeland.	1,037	Persistent	IQ (7-13; 38)	A drop from childhood to adult average full-scale IQ especially in adolescent-onset users.

Legend: in this table is offered an overview of longitudinal studies that expressly assess IQ before and after cannabis use.
Abbreviation: IQ: Intellectual Quotient. Ferraro et al. (*in press*). Modified.

However, authors did not have the opportunity to test the subjects after a period of abstinence of at least four weeks. Therefore, their findings are likely to be influenced by the residual effects of cannabis.

When looking at the results from above studies, it seems that premorbid IQ is linked to cannabis use, toward complex mechanisms.

Moreover, there are some important variables that have to be taken into account while studying the relationship between premorbid IQ and cannabis use: first of all, gender and the age at which cannabis consume started, socio-economic factors and, most significantly, frequency of cannabis use.

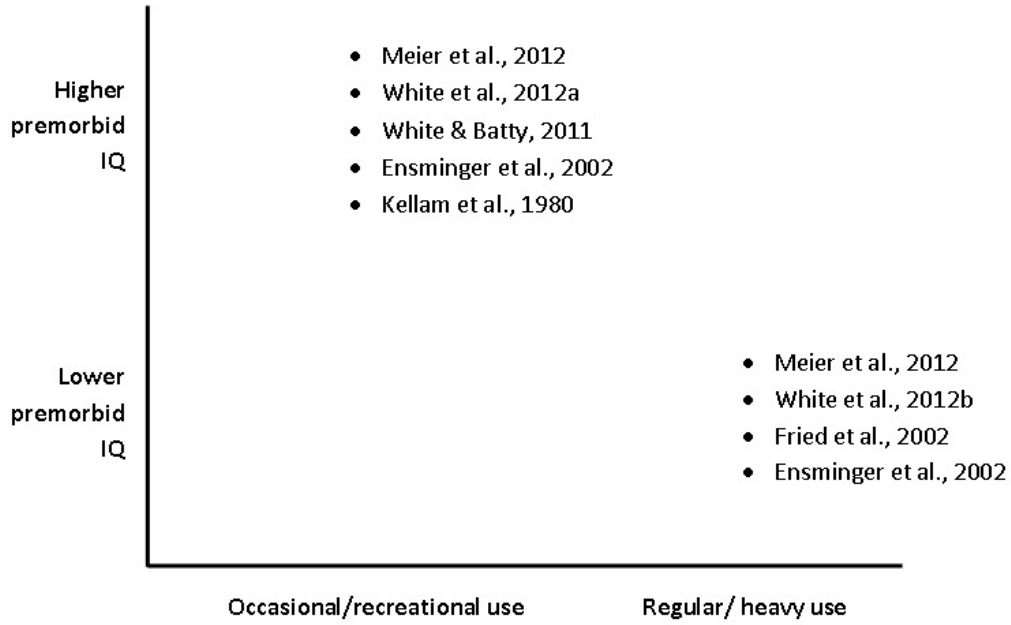
This study has raised a debate surrounding other potential confounders of the results. For example Rogeberg, (2013a) argues that socioeconomic status alone can potentially explain the IQ decline observed by Meier and colleagues and recalls the Flynn–Dickens model of IQ (Dickens et al., 2001) that emphasizes a two-way causality between IQ and environment with both a direct effect of the genotype on IQ and the opposite. That is, those with a higher IQ tend to seek out- or be sorted into more cognitively challenging environments that further increase IQ. Daly (2013) intervenes in the debate saying that the personality trait of "conscientiousness" may be protective for same people.

The cut and thrust of this debate is contained in two successive letters in the same volume of the *Proceedings of the National Academy of Science* (Moffitt, Meier, Caspi, & Poulton, 2013; Rogeberg, 2013b).

In a recent study, Power et al. (2015) divided a cohort of 1,237 participants with an established ICD-10 diagnosis of schizophrenia in non-users of cannabis and those with a lifetime history of cannabis use or dependency. They found no differences in premorbid cognitive ability between non-users of cannabis and those with a lifetime history of cannabis use or dependency, after controlling for age, age at onset of illness, and socio-economic status.

Interestingly, longitudinal studies present a point of consistence, as indicated in **Figure 7**, i.e. a relationship between higher premorbid IQ and recreational or discontinued use, though a lower premorbid IQ results as a predictor for regular or heavy cannabis use.

Figure 7. Premorbid IQ and Cannabis: Main Findings from Longitudinal Studies.



Legend: this graph provides a simplification of the results of longitudinal studies on premorbid IQ, categorized into "higher" and "lower" on the y-axis and differentiated by patterns of cannabis use, recreational versus regular use, in the x-axis. Ferraro et al. (*in press*).

6.3. Cannabis and Premorbid Adjustment: Enlarging the View

Longitudinal studies focused on different theories of predisposing factors to drug use and a number of variables have been identified.

The 1966-1967 first graders Woodlawn project (Kellam et al., 1980; Fleming et al., 1982; Ensminger et al., 2002), as already mentioned, enlarged their view to include social adaptive capacities, readiness-for-school and aggressiveness for males as risk factors and, alternatively, shyness and learning problems for girls as protective factors.

In a review of longitudinal studies on drug use, Wills, Walker, and Resko (2005) indicated some common risk and protective factors frequently identified in this field, as is shown in **Figure 8**.

Figure 8. Risk and Protective factors for Drug Use Mostly-Identified by longitudinal Studies (Wills, Walker & Resko, 2005).

Table 1. Summary of Risk and Protective Factors for Drug Abuse

Risk factors	Protective factors
• Parental substance use, abuse • Parental anger, mental health problems, antisocial personality • Low family attachment, family conflict • Early onset of use • Temperament: activity level, negative emotionality • Poor self-control (e.g., impulsiveness, disinhibition) • Risk taking, sensation seeking • Deviance-prone, unconventional attitudes (e.g., tolerance for deviance) • Life stress, racial discrimination • Externalizing symptomatology • Deviant peer affiliations • Motives for use • Availability of drugs • Neighborhood disorganization • Genetic factors	• Emotional, instrumental family support, family rules and organization • discipline and monitoring • Temperament: attentional focusing, positive emotionality • Good self-control (e.g., planfulness, executive functioning) • Conventional attitudes (e.g., value on achievement) • Perceived harmfulness of drugs • Moral beliefs • Resistance efficacy • Academic involvement • Perceived control, self-esteem, ethnic identity

Legend: this table is taken for exemplificative purpose from Wills TA, Walker C, Resko JA. Longitudinal studies of drug use and abuse. In: Sloboda Z, (ed.) Epidemiology of drug abuse. Springer; New York: 2005. pp. 177–192.

To summarize, the main fields of the interest are:

a) parental influence and familial relationships (parental problems, parental use of drugs, attachment vs. family support, discipline and monitoring);
b) poor self-control (externalizing symptoms, negative emotionality, impulsiveness, sensation seeking vs. the ability to plan life-activities (planfullness), executive functioning, attentional focusing);
c) life stress or discrimination *vs*. good self-esteem and ethnic identity;
d) deviant peer affiliation (deviance-prone, unconventional attitudes *vs*. conventional attitudes);
e) cultural context (availability of drugs, neighborhood disorganization *vs*. moral beliefs);
f) pattern of use (early onset, motive for use *vs*. perceived harmfulness of drugs, resistance efficacy);
g) academic involvement (poor *vs*. good);
h) genetic factors.

Verweij and colleagues (2010) carried out two meta-analysis (by distinguishing between males and females) of existing twin studies, in order to provide a more accurate estimate of the magnitude of genetic and environmental influences on cannabis use initiation and problematic cannabis use. The influence of genes in initiating cannabis use (results from the sum of allelic effects) was estimated to account for 48% of the variance for males (51% for problematic use) and 40% for females (59% for problematic use). Shared environment (family environment, prenatal influences, parental style and socio-economic status) explained the 25% of the variance in males (20% for problematic use) and 39% in females (15% only for problematic use); unshared environment (e.g. idiosyncratic events and experiences, unshared peers) accounted for 27% of the variance for males (29% for problematic use) and 21% of the variance in females (26% for problematic use). This study concludes that heritability is the most important factor in determining initiation and especially problematic use (with a substantial overlapping).

Furthermore, while the initial stages of the process of cannabis use are more sensitive to environmental factors (drug availability and use by peers), the likelihood of dependence could be more influenced by genetic factors (Verweij et al., 2010).

Genetic factors, coupled with early environment, could also explain temperamental attitudes and variables with more cognitive implications – poor self-control i.e. executive functions – that could, in turn, explain other risk-factors as, for example, deviant peer affiliation, lack of coping strategies and more lifetime stress. On the other hand, good self-control could have protective effects through promoting better academic competence (Novak & Clayton, 2001; Wills, Sandy, Yaeger, & Shinar, 2001; Wills & Stoolmiller, 2002).

For example, Wills and colleagues (2008) assessed planning and problem solving abilities in a 1,810 subjects baseline-sample – over the period from 11 to 15 years of age – as a buffering factor for the impact of three different risk factors: family life events (those occurring directly to a family member), adolescent life events (those occurring directly to the adolescent him/herself), and peer substance use (tobacco, alcohol, and marijuana). For each risk factor, subjects with higher scores on good

self-control showed less impact of that risk factor on their level of substance use, both concurrently and longitudinally (Wills, Ainette, Stoolmiller, Gibbons, & Shinar, 2008).

Once again, the impact on executive functions shown in studies on long-term cannabis effect (see **Figure 6**), could reflect some premorbid predisposition to cannabis use rather than a pure consequence of it. The impairment in executive functions could have consequences in the academic and the social adaptation fields by predisposing to a lesser capability to refuse the substance in a context where peers are using it (Wills et al., 2008). This could be useful in explaining the findings about premorbid social adjustment, IQ and premorbid academic adjustment, which are variables of interest in the context of this work.

6.3.1. Do Relationships Increase Opportunities for Cannabis Use?

Peer influence seems to be one of the most important predisposing factors to drug-use initiation (Bauman & Ennett, 1996; Vervaeke, van Deursen, & Korf, 2008). The idea that peer pressure in using drugs or peer selection is significant, has been sustained by different authors.

Peer influence has been shaped on a "social influence paradigm", which states that peers contribute to adolescent drug use by modeling drug use, by shaping norms, attitudes and values, and by providing opportunities and support for drug use (M. Allen, Donohue, Griffin, Ryan, & Turner, 2003; Chabrol, Mabila, Chauchard, Mantoulan, & Rousseau, 2008; Graham, Marks, & Hansen, 1991; Guxens, Nebot, Ariza, & Ochoa, 2007; Scherrer et al., 2008).

Bauman and Ennet (1996) have suggested that failure to control for selection effects, when examining the association between drug behaviours of friends and individuals' drug-use, may overestimate peer influence. In fact, friendships are also determined by drug use, i.e. drug users choose other users to be friends and *vice-versa*, thus reinforcing each other. Another reason of concern, in auto-reported data on friends' behaviour, is that adolescents tend to attribute their own choice to friends (Bauman & Ennett, 1996).

Peer selection has also been supported by a genetic-twin study (Gillespie, Neale, Jacobson, & Kendler, 2009) that collected data at three stages from 15 to 25 years. Authors suggested a direction to causality: a combination of genetic and environmental factors is able to explain inclination to cannabis use that, in turn, influences the liability to affiliate with deviant peers.

Both socialization and selection might provide crucial influence on adolescent in an interactive way (Simons-Morton & Farhat, 2010) especially in the context of different patterns of cannabis use.

6.3.2. Does School Prevent Individuals from Smoking Cannabis?

There are generally consistent findings among studies on the effects of cannabis that suggest that its early use reduces the likelihood of progressing further in formal education (Macleod et al., 2004; Townsend, Flisher, & King, 2007).

Linking to the abovementioned issue, Newcomb et al. (1988), surveyed participants from middle school, until young adulthood. Once more, social nonconformity predicted daily cannabis use, which anticipated a poor academic and vocational adjustment (Hays & Revetto, 1990; Newcomb & Bentler, 1988). However, the direction of this association has been an issue of debate.

While some studies suggest a link between academic failure and subsequent cannabis use (Apantaku-Olajide, James, & Smyth, 2014; Krohn, Lizotte, & Perez, 1997; Lee, Winters, & Wall, 2010), Fergusson's team controlled for several confounders and did not confirm this pathway (Fergusson & Horwood, 1997; Fergusson, Lynskey, & Horwood, 1996; Fergusson, Norwood, & Beautrais, 2003); they also suggested that it is likely that this association reflected the effects of the social context within which cannabis is used, rather than any direct effect of cannabis on cognitive ability or motivation, and that its effect is greater between frequent and early smokers (Fergusson et al., 2003). Esch and colleagues (2014) in a recent review of 51 studies, after controlling for socio-demographic, family and academic factors, found that adolescents who use cannabis before the age of 16

were up to five times more likely to drop out of secondary school than their peers who did not consume any drugs (Esch et al., 2014).

In a later review on this subject, Townsend and colleagues (2007) pointed out some potential confounders, such as social disadvantage or living in rural or urban area, difference in drop-out from school definitions and different measures of substance use across studies. Nevertheless, the main findings of the study indicated a largely consistent relationship between substance use and dropping out of high school, where the former preceded the latter (Townsend et al., 2007).

The problem of social disadvantage has been addressed specifically by Meier et al., (2015) who followed youth from an upper middle class community through the four years of high school, in order to rule-out the confounding effect of low socioeconomic status in the link between cannabis use and poorer academic performance. They confirmed the associations between cannabis use and inferior educational achievement and greater externalizing behavior, especially if the use was persistent through the four years of the study (Meier, Hill, Small, & Luthar, 2015). Nevertheless, this study was not able to disentangle the effect of cannabis and alcohol.

This question was recently studied by Silins et al. (2015), who examined three longitudinal studies from Australia and New Zealand. An at least weekly adolescent cannabis use was associated with two-fold increases in the odds of high school non-completion and university non-enrolment, and accounted for a greater proportion of variance than adolescent alcohol use (Silins et al., 2015).

Once again, could be interesting to examine separately cannabis abuse and cannabis recreational use, in relation to premorbid adjustment, in order to see the direction of this association.

7. Cannabis and Psychosis

Despite the failure to find a certain association between cannabis use and long-lasting detrimental effect on general IQ, it is very difficult to believe that a

psychotropic substance acting on the endocannabinoid system and through it important neurotransmitters such as acetylcholine, dopamine, GABA, glutamate, serotonin (Grotenhermen, 2004) does not have any neuropsychological effects in the long term.

Its effects may be so subtle that they are difficult to detect (Gonzalez, 2007), or alternatively cannabis may be relatively innocuous for most people, but quite toxic for the occasional individual (H. Pope, Gruber, Hudson, et al., 2001), depending on dose, type of cannabis used, of onset of use (Solowij & Pesa, 2010) gender (Crane et al., 2013), and genetic susceptibility.

Cannabis use is prevalent among people with first episode psychosis. One study in South London showed its use has increased markedly between 1965 and 1999, and disproportionately so compared to increase in cannabis use in other psychiatric disorders (Boydell et al., 2006). A recent meta-analysis reported an estimated prevalence of current cannabis use in people with first episode psychosis of 33.7% (35 samples, 95% confidence interval: 31%, 39%), with an initiation of regular use that starts 6.3 years before the onset of psychosis (10 samples, standardized mean difference = 1.56, 95% confidence interval: 1.40, 1.72) (Myles, Myles, & Large, 2016).

The causal association between cannabis use and psychosis was first formally studied by Andreasson and colleagues in 1987 (Andréasson, Engström, Allebeck, & Rydberg, 1987). Nowadays we know from subsequent replications of these results, that there are strong enough evidences of the fact that risk of psychosis is augmented by cannabis use (Moore et al., 2007; Potvin & Amar, 2008; Gage, Matthew, & Zammit, 2015).

Two meta-analyses estimated that cannabis consumption is associated with approximately twofold increased risk of developing a psychotic disorder (Henquet et al., 2005; Moore et al., 2007).

Cannabis may lead to an earlier age of onset of the illness and, interestingly, the difference by gender in age of onset appears to be reduced in cannabis users (Di Forti et al., 2009, 2014; Donoghue et al., 2014). An earlier onset of the disease is more likely if cannabis use starts in early adolescence, with a pattern of daily use of

high potency cannabis (Casadio et al., 2011; Di Forti et al., 2009, 2014; Large, 2011). In a recent analysis on patients aged 18-65 years, presenting to the *South London and Maudsley NHS Foundation Trust*, with first-episode psychosis, the population attributable fraction of first-episode psychosis for high-potency cannabis use was 24% (95% confidence interval: 17, 31) and much higher than the risk associated with use of hash (Di Forti et al., 2015). That means that a portion of psychosis could be prevented if heavy cannabis use was avoided (Di Forti et al., 2015). Van Os and colleagues reported a three times higher risk of developing psychotic symptoms in the general population, associated to cannabis consumption (NEMESIS study, van Os et al., 2002). Experiments, have shown that healthy people who are administered THC intravenously are more likely to develop transient psychotic-like experiences (Morrison et al., 2009) and that THC worsens psychotic symptoms in people suffering from psychosis (D'Souza et al., 2004).

In summary, cannabis use is responsible for an increased risk of both the onset of psychosis in previously psychosis-free people (Murray & Di Forti, 2016) and poor prognosis for those with an established vulnerability to psychotic disorder (van Os, 2002; Schoeler et al, 2015).

Individual predisposing genetic factors that increase vulnerability, or resilience, to the effects of cannabis have been reported to include a functional polymorphism in the catechol-O-methyltransferase (COMT Val^{158}Met) gene (which has a role in the catabolism of dopamine in the prefrontal cortex) along. However, this mechanism is not fully understood and remains controversial. Another suggestion concerns genetic variation at rs2494732 of AKT1 (involved in the dopamine neurotransmission) as influencing the risk of developing a psychotic disorder in cannabis users (Di Forti et al., 2012; van Winkel, 2011). Another study indicated that a variant in the dopamine D_2 receptor gene may also increase psychosis risk (Colizzi et al., 2015). These two mechanisms, involving postsynaptic genes, are compatible with the hypothesis of a postsynaptic supersensitivity in cannabis-related psychosis (Murray, Mehta, & Di Forti, 2014).

A recent meta-analysis on a sample of over 32,000 individuals from genome-wide association studies (GWAS), has identified four genes as involved in lifetime

cannabis use (*NCAM1*, *CADM2*, *SCOC* and *KCNT2*) with a high degree of genetic sharing with lifetime cigarette smoking (Stringer et al., 2016).

A pattern of genetic vulnerability to psychosis could also predispose subjects to cannabis use, as was suggested in a recent study on 2,082 healthy individuals conducted by Power and colleagues (R. A. Power et al., 2014), but further studies are required to clarifying this question.

7.1. Cannabis, Psychosis and IQ

Surprisingly, three different meta-analyses on cognition and cannabis, among schizophrenic patients, found better cognitive performance in patients with a lifetime use of cannabis (Potvin et al., 2008; Rabin et al., 2011; Yücel et al., 2012). This counterintuitive finding, coupled with the fact that most psychotic patients suffer from cognitive impairment (Reichenberg et al., 2009) make it more difficult to understand the relatioinship between these two risk factors.

Two different explanations have been advanced for this finding. The first suggests that those psychotic subjects who use cannabis have less premorbid cognitive impairment than those who do not. This could be because good premorbid functioning is necessary to acquire and sustain an illegal drug habit (Joyal et al., 2003; Rodríguez-Sánchez et al., 2010; Stirling et al., 2005) or because cannabis use increases the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability (de la Serna et al., 2010; Ferraro et al., 2013; Leeson, Harrison, et al., 2011; Løberg & Hugdahl, 2009; Schnell et al., 2012, 2009; Yücel et al., 2012).

A second possible explanation, based on research in vitro and in vivo into animal models of Parkinson's disease and Alzheimer's disease, suggests that some cannabinoids (i.e. CBD) have a neuroprotective action by activating CB-receptors that possesse anti-inflammatory properties and inhibits microglia-mediated oxidative stress (Binukumar et al., 2015; Chung et al., 2011; Gómez-Gálvez et al., 2016; Martín-Moreno et al., 2011; Ramírez et al., 2005), which may help to prevent psychosis-related cognitive decline (Jockers-Scherübl et al., 2007; Løberg &

Hugdahl, 2009). For example Martín-Moreno et al. (2011) showed that CBD, after subchronic administration for 3 weeks, was able to prevent learning of a spatial navigation task and cytokine gene expression in β-amyloid-injected mice, by modulating microglial cell function. Gómez-Gálvez et al. (2016) provided evidences on the up-regulation of CB2 receptors in glial elements in postmortem tissues of PD patients, in relation with the activation of microglial cells and also towards certain capability of these cells to generate proinflammatory factors.

This alternative explanation has recently gained greater attention from considering the CBD component as part of the treatment in several neurological disorders, such as multiple sclerosis, neurodegenerative disorders and stroke, pain treatment, epilepsy, dystonia, and tics, but also anxiety, drug abuse, autism and schizophrenia (for a deepest look see *Cannabinoids in the Treatment of Neurological Disorders*, by Devinsky, Whalley, & Di Marzo, 2015).

Furthermore, an increasing number of human studies have been performed to provide insight into the antipsychotic properties of CBD (Iseger & Bossong, 2015; Schubart et al., 2014; Zuardi et al., 2012). It has been reported that pre-treatment with CBD inhibits THC-elicited psychosis and cognitive impairment in healthy subjects (Englund et al., 2013). In fact, Δ-9-THC and CBD can have opposite effects on regional brain function, which might underlie different symptomatic and behavioural effects, and CBD's ability to block the psychotogenic effects of Δ-9-THC (S. Bhattacharyya et al., 2010).

Data observation suggests that while studies on animal models could precisely measure the proportion between Tetrahydrocannabinol (THC) and Cannabidiol (CBD), types of cannabis that are encountered by real-world users have a wide range of THC:CBD ratios (R. J. M. Niesink & van Laar, 2013).

A recent report suggest that adolescents (13-18 years old) engaged in regular marijuana use can raise their expected odds of experiencing subsequent subclinical psychotic symptoms up to 133% and this effect can persist even when they stopped using marijuana for at least one year (Bechtold, Hipwell, Lewis, Loeber, & Pardini, 2016). Also, healthy people who smoke higher THC concentration cannabis are more likely to develop psychosis-like symptoms (like for example paranoia) (C. J.

A. Morgan & Curran, 2008) even with a recreational pattern of use (Craig Morgan et al., 2012). Additionally, among the tiny percentage of smokers who develop psychosis, the increasingly preferred variety used is skunk (Di Forti et al., 2009), which has a relatively high concentration of THC.

Therefore, there is not enough evidence to sustain the possibility that paradoxical effects of recreational cannabis use, frequently observed in naturalistic studies with psychotic patients, are derived from a neuroprotective action of CBD on the brain.

Other insights, regarding the first of the two hypothesis, are provided from studies that report that different patterns of cannabis use are differently related to cognition, i.e. that any lifetime use of cannabis is associated with a better cognitive performance (Meijer et al., 2012; Rabin et al., 2011; Yücel et al., 2012), while current cannabis use is associated with poorer performance (Meijer et al., 2012). Buchy and colleagues (2015) have recently suggested that people at clinical high risk for psychosis, who were late-onset users, showed significantly higher IQ than those who were early-onset users (Buchy et al., 2015).

These data suggest that, age at onset of cannabis or frequency of its use may be important factors for IQ, and that lifetime cannabis-using individuals might constitute a subgroup with a higher cognitive potential.

7.2. Cannabis, Psychosis and Premorbid IQ

To my knowledge, only one study (Leeson, Harrison, et al., 2011) has found higher premorbid IQ in patients who smoked cannabis –among 99 subjects at their first episode of psychosis– using the *Wechsler Test of Adult Reading* (WTAR) (Holdnack, 2001) as an estimated measure of premorbid IQ. Other studies (DeRosse, Kaplan, Burdick, Lencz, & Malhotra, 2010; Helle et al., 2015; Jockers-Scherübl et al., 2007; Ringen et al., 2013; Sevy et al., 2007; Tosato et al., 2013; Yücel et al., 2012) that have incidentally examined premorbid IQ in psychosis in relation to cannabis use have reported inconsistent findings, probably due to their small sample size and other methodological problems. In a recent pilot study (in Chapter 4), my colleagues and I found strong evidence for a better IQ, a better

premorbid IQ and a minor deterioration in IQ from premorbid IQ in FEP patients who had used cannabis in their lifetime (Ferraro et al., 2013).

7.3. Cannabis, Psychosis and Premorbid Adjustment

Cognition has been established as a predictor of real world community functioning in schizophrenia (Evans et al., 2003; M. F. Green et al., 2000).

However, studies on the relationship between cannabis use and neurocognitive functioning in psychosis, which have controlled for the potential bias of premorbid functioning, are rarely represented in this context and often inconclusive.

Ringen et al. (2013), in a naturalistic study of 364 patients with schizophrenia spectrum disorder – from catchment areas in Oslo, Norway – reported that cannabis use, detected in the urine of 21 patients, was associated with significant dysfunction in several neurocognitive domains, independent of a current diagnosis of cannabis abuse. However, level of premorbid functioning explained the associations for all measures. They concluded that differences in premorbid functioning may explain apparent differences in neurocognitive function between schizophrenia spectrum patients using cannabis or not and that illness-related traits, present early in life, can affect both later cannabis use and neurocognition (Ringen et al., 2013).

Gonzalez-Blanch et al. (2015) suggested that cannabis misuse (defined as meeting DSM-IV-TR criteria for cannabis abuse or dependence) is not associated with social functioning at baseline. Nevertheless, over a 30-month follow-up, first episode psychosis patients without cannabis use disorder showed significant improvements in their social functioning, whereas patients with cannabis misuse at baseline displayed no such improvement. They adjusted their analysis for potential confounders, such as age, gender, negative symptoms, premorbid functioning, DSM-IV diagnoses, baseline social functioning and other substance use (González-Blanch et al., 2015). Both these studies, have found worse actual and premorbid social functioning in patients with current or heavy cannabis use. Conversely, Sevy et al., (2010) have incidentally found among 49 first-episode schizophrenia subjects with cannabis use disorder (cannabis abuse or dependence), that use of cannabis

commonly started before the onset of positive symptoms and that subjects were predominantly male, younger at study entry, had a better premorbid childhood social adjustment, a trend for poorer premorbid childhood academic adjustment, earlier age at onset of positive symptoms, less educational attainment, a lower self-socioeconomic status, less motor abnormalities but more severe hallucinations and delusions, compared to non-substance abusing subjects (Sevy et al., 2010). In line with these findings, Compton et al., (2011) reported that psychotic patients having used cannabis at ≤15 years, had better social functioning in their early adolescence than those who had not, whilst those who had used cannabis later, but before 18 years, had poorer late adolescence academic functioning (Compton, Broussard, Ramsay, & Stewart, 2011). Neither of these two studies considered cognition, so it is difficult to establish a continuity of their finding with those reporting a better IQ in psychotic patients who used cannabis. Furthermore, they report a worse academic adjustment, which remains unexplained.

In conclusion, current cognitive abilities of subjects who smoked cannabis are reliable only if assessed after a prolonged time of abstinence. Eventual long-term impairment observed after this period could reflect the consequence of a complex premorbid gene-early environmental predisposition.

This predisposition can influence the initial contact with the substance and a particular pattern of cannabis use, moderated by other environmental factors. This could be true even for clinical samples since, according to the neurodevelopmental theory of schizophrenia (Murray & Lewis, 1987), the neurocognitive impairment in psychosis remains stable after the onset of the illness (Bora & Murray, 2014). Similarities between clinical and non-clinical samples are also given from the fact that patients with psychosis use cannabis for the same reasons the general population does, to "get high", relax and have fun (Kolliakou, Joseph, Ismail, Atakan, & Murray, 2011), but also for affect regulation and socialization (Dekker, Linszen, & De Haan, 2009; B. Green et al., 2004).

Some of these points will be taken into account and further examined by generating the hypothesis of this work of thesis in the next chapter.

Chapter 2

Aims and Hypotheses

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1. Introduction

Following on the literature just reviewed, studies on cannabis use and cognitive impairment associated with schizophrenia have mostly reported better cognitive performance among patients with psychosis who have used cannabis than in those who have not.

The main objective of the work presented in this thesis is to explore this association in an epidemiologically-derived case-control study in a sample derived from *The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions* (EU-GEI) and to address some unresolved issues.

I will now clarify the hypotheses and the aims of my Thesis.

2. Thesis Aims and Hypotheses

As discussed in the previous chapter, two different explanations have been advanced for this counterintuitive finding: a "premorbid-driven hypothesis" and a "neuroprotective-derived hypothesis".

In this work of Thesis, I am going to test the first of these two hypotheses, with the aim of exploring IQ and premorbid conditions and how they are related to cannabis use in patients at their first episode of psychosis (FEP), by comparing those cannabis using patients to non-users and to their respective healthy controls.

The main hypothesis is that psychotic patients who used cannabis in their lifetime have higher IQ scores and better premorbid adjustment than those who do not, depending from their pattern of cannabis use, as is better listed below.

2.1. Data derived from different Countries

Given that the prevalence, and patterns, of cannabis use are culturally driven, I wanted to study FEP cannabis-using and non-using cases and controls coming from different European countries (United Kingdom, Italy, Spain, France, Netherlands) as part of the EU-GEI study. I expect that "Country" will significantly affect the relationships between the variables of interest.

2.2. Cognition and premorbid adjustment of cases compared to controls

To compare IQ scores in cases and controls. I expect that cases will show a greater cognitive impairment (i.e. lower IQ) than controls overall, independent of potential confounders and across all countries.

To analyse the main two components of the premorbid adjustment scores (Premorbid Social Adjustment and Premorbid Academic adjustment) (D. N. Allen et al., 2001; Barajas et al., 2013), i.e. the Premorbid Academic Factor (PAF) and the Premorbid Social Factor (PSF) and to compare them in cases and controls.

I expect that cases will be more socially and academically impaired in their premorbid period (i.e. before 16 years) than controls overall, independent of potential confounders and across all countries.

2.3. Pattern of cannabis use of cases compared to controls

To compare pattern of cannabis use (i.e. lifetime prevalence, frequency, age at first use, current use, mode of use, etc.) of cases and controls.

I expect that cases will be more likely to have smoked high potency cannabis, starting at an earlier age and with a higher frequency overall (Di Forti et al., 2014).

2.4. IQ and premorbid adjustment in cases that used cannabis in their lifetime compared to those who did not and to their respective healthy controls

To compare the main effects and interaction terms of lifetime cannabis use (yes/no) and group belonging (cases or controls) on IQ, PAF and PSF scores (i.e. three different ANCOVAs).

I expect that cases who used cannabis in their lifetime will be less cognitively impaired (i.e. higher IQ) than those who did not, independent from potential confounders. I also expect that they will show a better premorbid adjustment.

2.5. Premorbid adjustment and IQ in cases who never used cannabis in their lifetime compared to those who used cannabis on a daily basis or less than everyday and to their respective healthy controls

To cluster the sample according to "frequency of cannabis use".

To compare the main effects and the interactions terms of cannabis use, by frequency (never, less frequently than everyday and everyday) and group (case or controls) on IQ, premorbid social (PSF) and academic adjustment (PAF) scores (i.e. one MANOVA with three outcomes, controlled for sociodemographic main variables and Country). I expect to find a better premorbid adjustment (both social and academic) in cases who smoked cannabis in their lifetime "less frequently than everyday", compared to people who smoked cannabis "everyday" and to people who did not smoke cannabis at all in their lifetime.

The final aim of this work is to identify the relationship between IQ, premorbid social and academic adjustment with cannabis use in psychotic patients, compared to healthy controls, in order to be able to explain in which cases you can expect a better IQ and a better premorbid adjustment and why.

I hypothesize a subgroup of patients with a recreational use of cannabis, who are less cognitively impaired at the onset and less socially withdrawn in the premorbid period than other patients.

Chapter 3

Methods and Statistical Analyses

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1. Introduction

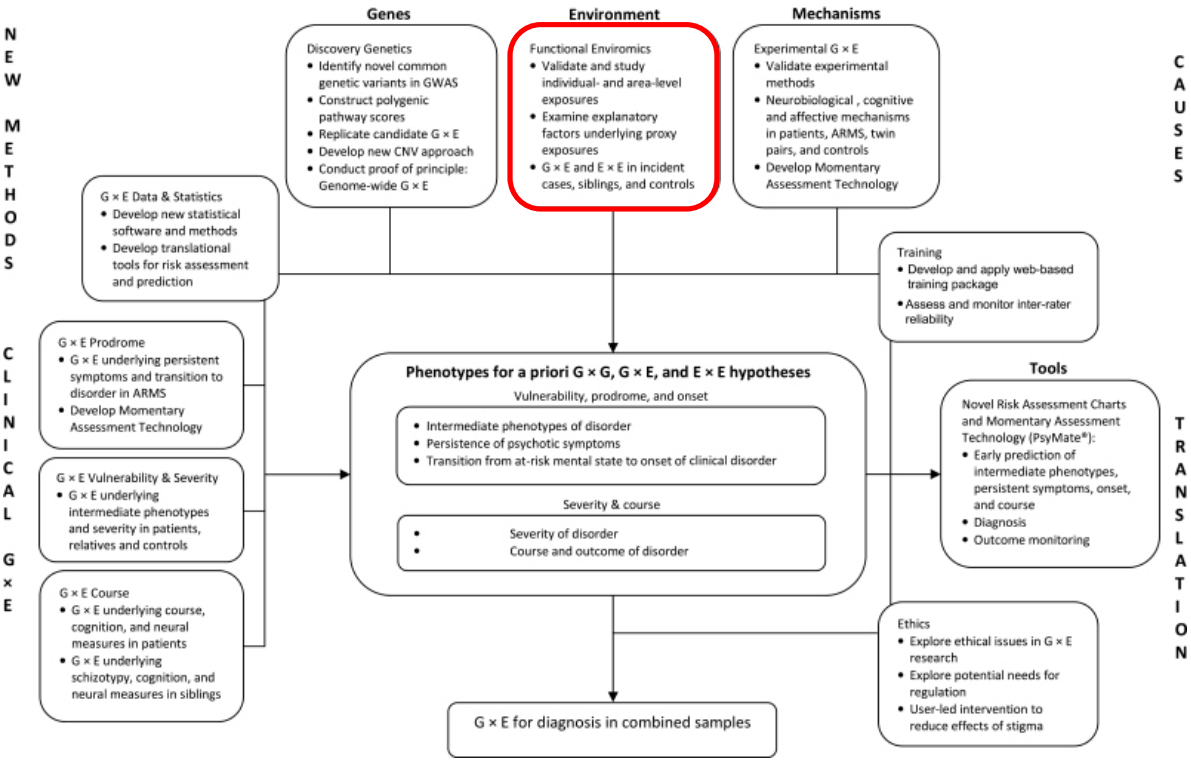
In this chapter I will outline the general methodology for the study, run in different European Countries, where patients and controls were recruited from the 1st of May 2010 to 30th of June 2015. This work was born because of the interest in, and thanks to the collaboration with two research studies conducted at the Institute of Psychiatry, Psychology and Neurosceince, King's College of London: *Genetic and Psychosis* (GAP) study and *The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions* (EU-GEI) project. Both these studies have been also conducted in Palermo, in which I had the opportunity to be involved, as part of the research team. In 2008, the Psychiatric Section of Palermo University Department of "*Biomedicina Sperimentale e Neuroscienze Cliniche*" (Bionec), started the *Sicilian Genetic and Psychosis* (SGAP) project, an incidence and a case control study aimed at: a) collecting epidemiological data on the incidence of psychotic disorders in Palermo and at b) identifying the role of putative environmental and genetic risk factors in the risk of developing psychoses. In 2010 the Palermo research team joined the EU-GEI, one of the largest European first episode psychosis studies, investigating the interaction between genetic and environmental factors potentially involved in increasing the risk of psychotic disorders (www.eu-gei.eu). The pilot study (Chapter 4) was framed into the first of these two studies (SGAP), while the present work of thesis forms part of the EU-GEI study, which will be presented in the next paragraph.

2. The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Project (EU-GEI)

The aim of EU-GEI is to identify, over a 5-year period, the interactive genetic, clinical and environmental determinants involved in the development, severity and outcome of schizophrenia. EU-GEI has employed family-based, multidisciplinary research paradigms. The overall aim of EU-GEI is the identification and translational application of clinical, genetic, and environmental interactions in the development, severity, and course of schizophrenia in patients and their families.

To this end, several work packages have been established, and expertise from multiple disciplines has been focussed on addressing contemporary challenges in G × E research (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) et al., 2014) (see **Figure 9**).

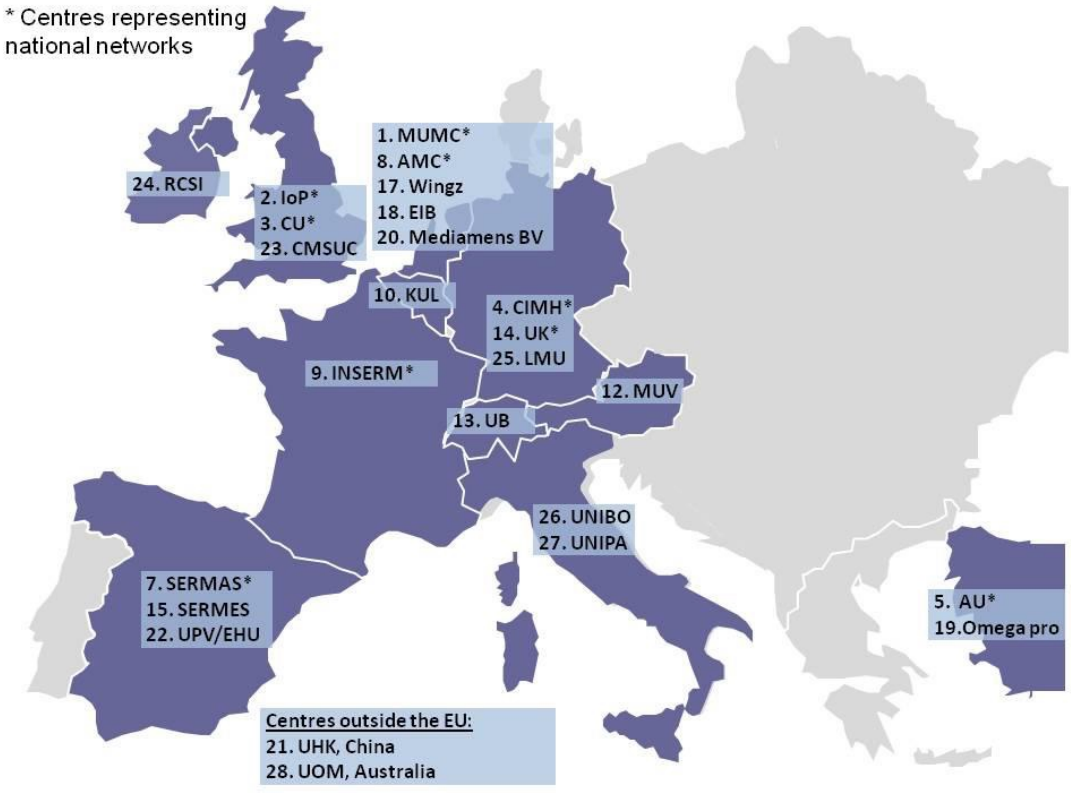
Figure 9. General Approach and Overview of the EU-GEI project.



Legend: the red square identifies the Work Package in which is framed the aim of this work of thesis (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) et al., 2014)

In order to reach these goals, EU-GEI has assembled a multidisciplinary team of top schizophrenia researchers (by a Consortium Agreement), who have the range of skills required to deliver a program of research and who have access to collect a number of unique European samples. (Project Final report, version 30.06.2015, in: www.eu-gei.eu). The project was organized and coordinated by Professor Jim Van Os (University of Maastricht). The partners in EU-GEI represent the nationally funded schizophrenia/mental health networks of more than 15 European and non-European countries (EU-GEI affiliated centers) (see **Figure 10**).

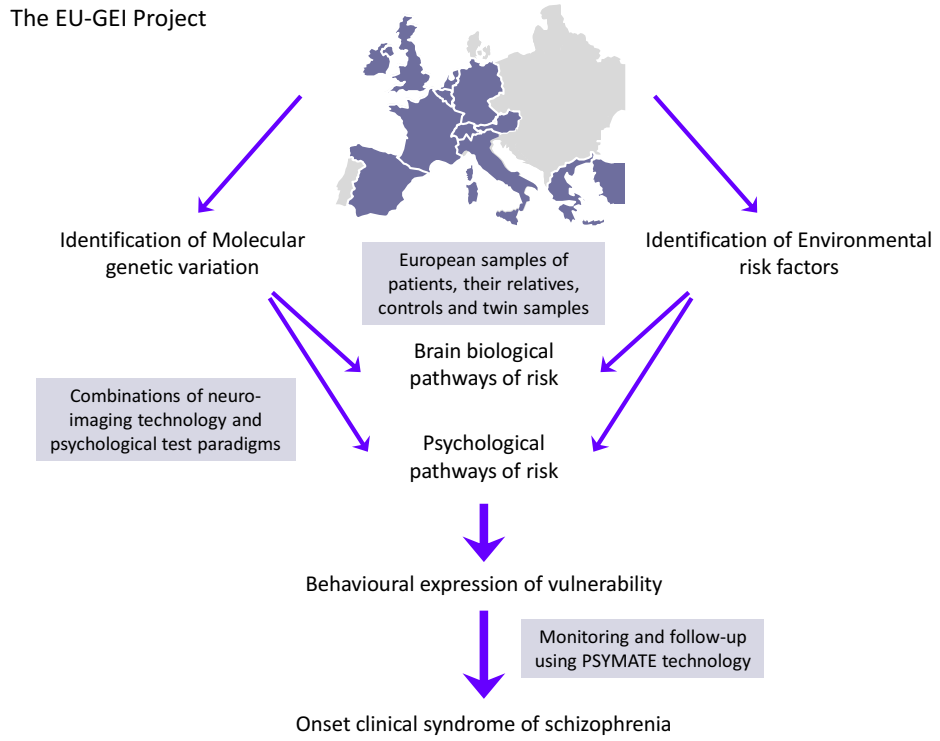
Figure 10. Map of Partners in EU-GEI project. All Work Packages.



Legend: **P1 - Universiteit Maastricht / MUMC** Prof. Jim van Os (Coordinator) Dr. Bart Rutten (Vice-Coordinator); **P2 - King's College London / IoP** Prof. Philip McGuire (WP5 leader) Craig Morgan (WP2 leader); **P3 - Cardiff University / CU** Prof. Michael O'Donovan (WP3 leader); **P4 - Central Institute of Mental Health / CIMH** Prof. Andreas Meyer-Lindenberg (WP4 leader); **P5 - Ankara Universitesi / AU** Prof. Meram Saka (WP6 leader); **P7 - Servicio Madrileño de Salud / SERMAS** Dr. Celso Arango (WP10 leader); **P8 - Academisch Medisch Centrum – Universiteit van Amsterdam / AMC** Prof. Lieuwe de Haan (WP11 leader); **P9 - Institut National de la Santé et de la Recherche Medicale / INSERM** Prof. Marion Leboyer; **P10 - Katholieke Universiteit Leuven / KU** Leuven Prof. Marc De Hert; **P11 - University Mental Health Research Institute / UMHRI** Prof. Nicholas Stefanis; **P12 - Medizinische Universität Wien / MUW** Prof. Gabriele Sachs; **P13 - Universität Basel / UB** Prof. Anita Riecher-Rössler; **P14 - Universität zu Köln – Universitätsklinikum / UK** Prof. Joachim Klosterkötter; **P15 - SERMES Planificacion / SERMES** Dr. Antonio Berlanga; **P17 - Wingz b.v. / WINGZ** John Veeren; **P18 - E.C.S. International BV / EIB** Peter Emonds; **P19 - Omega Pro Proje Arastirma Gelistirme ve Danismanlik Ltd Þti / Omega Pro** Dr. Murat Hayran; **P20 - Mediamens B.V.** / **Mediamens** Daniëlle Dohmen; **P21 - The University of Hong Kong / UHK** Prof. Pak Chung Sham (WP8 leader); **P22 - Universidad del Pais Vasco / UPV-EHU** Dr. Aitzibar Emaldi (WP9 leader); **P23 - The Chancellor, Masters and Scholars of the University of Cambridge / CMSUC** Prof. Peter Jones, Dr James Kirkbirde; **P24 - Royal College of Surgeons in Ireland / RCSI** Prof. Mary Cannon; **P25 - Ludwig-Maximilians-Universität München / LMU** Prof. Dan Rujescu; **P26 - Alma Mater Studiorum – Universita di Bologna / UNIBO** Prof. Ilaria Tarricone; P27 - **Universita Degli Studi di Palermo / UNIPA** Prof. Daniele La Barbera; **P28 - University of Melbourne / UOM** Prof. Patrick McGorry. **Project Final report, version 30.06.2015, in: www.eu-gei.eu.**

The project was funded by the European Community's Seventh Framework Programme, under grant agreement No. HEALTH-F2-2010-241909 (Project EU-GEI). The specific outline of the project is shown in **Figure 11**: it is focused on the effects of gene-environment interactions on brain pathways and psychological vulnerability, and how these cerebral and psychological pathways mediate subtle, but measurable, behavioural expressions of vulnerability for psychotic disorder.

Figure 11. Outline of the EU-GEI project.



(EU-GEI general press, in www.eu-gei.edu)

An important aspect of the project is the development of tools that allow for the actual measurement of the behavioural expression of vulnerability that is caused by gene-environment interactions. This makes it possible to monitor, and possibly modify, vulnerability at the behavioural level, thus preventing transition to overt illness. For example, European enterprises and start-ups in EU-GEI are working on new technologies (i.e. PSYMATE) allowing for momentary assessment of subtle alterations in mood, thinking, perception and volition in response to small stressors in the flow of daily life for patients. (EU-GEI, 2009-gei.edu).

3. Study design

This is a case-control design where cases are individuals with a first episode of psychosis (FEP) and controls are individuals without psychosis recruited from the same geographical area as the cases.

This work of this Thesis framed into the Work Package 2 of the project, the "Functional Enviromics" that was specifically designed to generate, in each site, samples of first episode cases and of population based controls with extensive information on exposure to a full range of environmental factors, and their interaction across the life course on odds (risk) of psychotic disorder. It has developed and applied methods for the detailed assessment of candidate, individual- and area-level environmental exposures of public health relevance.

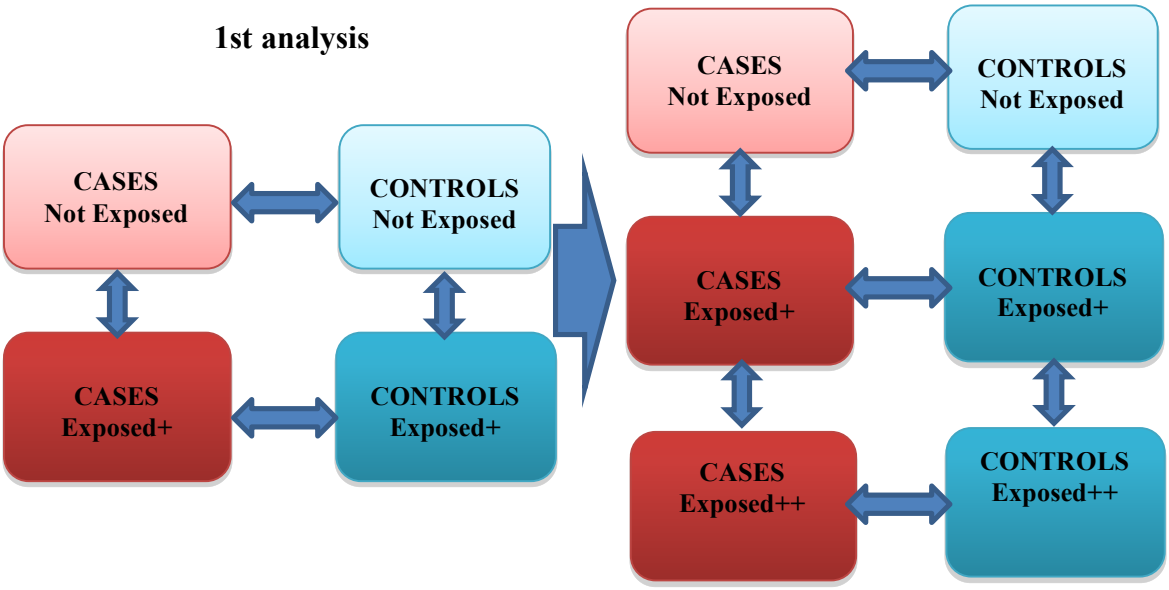
This work package further aims, together with "Discovery Genetics" and "G × E Data & Statistics," to examine evidence for hypothesized genes x environment G × E and environment × environment (E × E) interactions, the latter being the framework for this work (see **Figure 9**) (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) et al., 2014).

2,553 incident cases were identified across all sites. This constitutes the largest and most extensive case-control study of first episode psychosis ever conducted (Project Final report, version 30.06.2015, in: www.eu-gei.eu).

For the purpose of this study, the main analyses are conducted firstly on cases and controls exposed or not exposed to the risk factor of cannabis use and secondly on cases and controls separated according with different pattern of frequency, as is shown in **Figure 12**.

Premorbid adjustment and IQ were considered as continuous measures, that result from a Gene-Environment Correlation – *rGE* (Jim van Os, Rutten, & Poulton, 2008) and therefore have been used as main outcomes of this model.

Figure 12. Study Design.



Legend: The figure describes the study design, a case control study where firstly patients and controls exposed *vs*. not exposed to the risk-factor of cannabis use are compared each other and secondly, different levels of cannabis exposure are considered in this comparison.

4. Cases

Cases were defined as people resident within a clearly defined catchment (study) area for a period of at least 6 months, aged 18-64 years and affected by a first episode of psychosis (even if long-standing) with a diagnosis of schizophrenia (F20); other non-affective psychoses (Schizophreniform disorder - F21; Delusional disorder - F22; Brief psychotic disorder - F23; Schizoaffective disorder - F25; Psychotic disorder not otherwise specified - F28, F29) or affective psychosis (Bipolar disorder with psychotic features - F312, F315; Major depressive disorder with psychotic features - F323, F333) (World Health Organization, 1992) during the study period. We excluded subjects with evidence of psychotic symptoms precipitated by an organic cause or transient psychotic symptoms resulting from acute intoxication as defined by ICD-10, illegal migrant or people who have received a treatment with anti-psychotic medication for an episode of psychosis outside of the study period (See **Table 5**). Age at first onset was defined as the age the subject had at the time of the first access to psychiatric services.

Table 5. Inclusion and Exclusion Criteria for Cases.

Cases Inclusion
1. Age 18 to 64.
2. Resident within a clearly defined catchment (study) area for a period of at least 6 months.
3. Presence of an untreated first episode of psychosis (even if long-standing) (ICD-10: F20-29; F30-33 [psychosis codings]) during the study period.
Cases Exclusion
1. Age under 18 or over 64
2. Resident within a clearly defined catchment (study) area for a period of less than 6 months.
3. Treatment with anti-psychotic medication for an episode of psychosis outside of the study period.
4. Evidence of psychotic symptoms precipitated by an organic cause.
5. Transient psychotic symptoms resulting from acute intoxication as defined by ICD-10.
6. Illegal migrant (i.e., no legal right to remain in country).

Project Final report, version 30.06.2015, in: www.eu-gei.eu.

A screening was run on all the subjects aged 18 to 64 years old with a first episode of psychosis (defined as the first contact with any psychiatrist) presenting from the 1st of May 2010 to 30th of June 2015 at the mental health services of each catchment area. For example, the catchment area in Palermo was the whole city. All inpatient units (five), private psychiatric hospitals (four) and outpatient services (five) were examined through a weekly contact.

The five inpatients and the five outpatients units in Palermo are part of the public regional mental health service system (Azienda Sanitaria Provinciale of Palermo, Azienda Ospedaliera Universitaria Policlinico, Azienda Ospedale Civico ARNAS, Azienda Ospedali Riuniti Villa Sofia e Ospedale Cervello) while four private hospitals (Villa Margherita, Villa Serena, Casa di Cura d'Anna, Casa di Cura Stagno) are private psychiatric clinics which are in the network of the regional public mental health system. All people can receive care in both public and private units because they don't have to pay to receive psychiatric care.

5. Controls

During the same study period, a control group of healthy volunteers was recruited from the local population living in the same catchment area, through a quota sampling able to collect a control group rapresentative of the general population in that area.

Controls were aged 18 to 64, resident within a clearly defined catchment (study) area for a period of at least 6 months (the same as the cases) and had not evidence of current or past psychosis (including treatment with antipsychotic medication), otherwise they were excluded (See **Table 6**).

Table 6. Inclusion and Exclusion Criteria for Cases.

Controls Inclusion
1. Age 18 to 64.
2. Resident within a clearly defined catchment (study) area for a period of at least 6 months.
3. No evidence of current or past psychosis (including treatment with antipsychotic medication).
Exclusion
1. Age under 18 or over 64.
2. Resident within a clearly defined catchment (study) area for a period of less than 6 months.
3. Current or past psychotic disorder (or treatment within antipsychotic) (including diagnosis or treatment within time frame of the study).
4. Illegal migrant (i.e., no legal right to remain in country).

Project Final report, version 30.06.2015, in: www.eu-gei.eu.

The recruitment of controls was advertised through Internet, newspaper advertisements, leaflets placed in churches, gyms, private residences (by local community survey, using publicly available household lists as sampling frames) and previous databases of volunteers, using quota sampling to ensure they were broadly representative of the population at risk in terms of age, gender, migrant status, level of education and employment status.

Quota sampling basically segments the catchment (study) area population (using population statistics) to determine the proportion of the local population in certain categories (e.g. gender, age, etnicity). This is then used to set quotas for the number of controls to be recruited in each category.

6. Methods and Instruments

The assessment was translated in the appropriate language for each Country and delivered in a proper private setting. Instruments were distributed online on the interactive official website (www.eu-gei.eu) for each Country and interrater reliability videos and tools were available at regular times (i.e. once a year or more frequently), in conjunction with Work Package 9 (dedicated to the Training) and a Kappa >70 was considered acceptable.

When a subject satisfying the inclusion criteria was identified, he/she was invited to be enrolled in the study and after signing a consent form he/she went through the whole assessment. When the subject didn't give the consent to be enrolled or he/she was unavailable to be asked for consent, his/her main clinical and socio-demographic data were still recorded anonymously in a specific form (e.g. in Palermo, it was done according to the Italian law about the general authorization to process personal data for scientific research purposes) (Gazzetta Ufficiale della Repubblica Italiana, n° 72, 26 March 2012). Medical records were checked in detail to collect clinical and socio-demographic information for those who didn't go through the whole assessment and subsequently included into the incidence group.

The instruments used for the assessment are described below.

6.1. Modified version of the Medical Research Council Scale (MRC)

The Modified version of the Medical Research Council (MRC) socio-demographic scale (Mallett, Leff, Bhugra, Pang, & Zhao, 2002) was used to collect the main socio-demographic data (such as age, gender, ethnicity, place of birth, housing and living circumstances, level of education, years of education, occupation etc.) (See **Appendix I**).

6.2. Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT)

Diagnoses, first ascertained by clinicians, were operationalized trough the OPCRIT system (McGuffin, Farmer, & Harvey, 1991) (see **Appendix II**) a 90-item operational criteria checklist for psychosis and a computer program designed for the usage in conjunction with it. It includes a structured clinical interview with questions and optional probes derived from the *World Health Organization Schedules for Clinical Assessment in Neuropsychiatry* (SCAN, version 2.1).

This provides a simple and reliable method of applying multiple operational diagnostic criteria in studies of psychotic and affective diseases to facilitate a polydiagnostic approach to mental illness.

6.3. Cannabis Experience Questionnaire modified version (CEQmv) + CIDI

Detailed data on cannabis and other illicit drugs consumption were collected by the Cannabis Experience Questionnaire modified version, CEQmv (Di Forti et al., 2009) to investigate qualitative and quantitative information on cannabis (age at first use, frequency, duration of use in years, current or past use etc.) including a section from Composite International Diagnostic Interview (CIDI) on other substances of abuse, and tobacco and alcohol use (Kishore, Kapoor, & Reddaiah, 1999) (see **Appendix III**).

6.4. Wechsler Adult Intelligence Scale (WAIS) – abbreviated version

An abbreviated version of the WAIS, adapted from the most recent version available in each country from Ryan et al. (1998) was used in cases and controls in order to estimate IQ scores. All versions included Digit Symbol substitution, Arithmetic, Block Design and Information subtests from which raw and scaled scores were derived. An estimated sum of scaled scores was calculated from the sum of scaled scores (11/4* sum of scaled scores) and then converted to IQ (see **Appendix IV**).

6.5. Premorbid Adjustment Scale (PAS) – reduced version

An abbreviated version of the *Premorbid Adjustment Scale* (Cannon-Spoor et al., 1982) was adapted in each language. The scale was divided into two distinct developmental age periods: childhood to age 11 and early adolescence (i.e. 12 to age 16). Individual items in the childhood and adolescence categories assess premorbid adjustment by asking about sociability and social withdrawal, peer relationships, scholastic performance, adaptation to school, and ability to form socio-sexual relationships (after 16 years). Rating was from 0 (not withdrawn) to 6 (withdrawn) for a total of 9 different scores (see **Appendix V**).

7. Data manipulation

SPSS (version 22) was used to build the dataset including all the variables of interest for the analyses. All statistical analyses were conducted using SPSS 22 and STATA 14.

First of all, a reverse-score of Premorbid Adjustment Scale (PAS) was obtained, in order to have higher scores for better adjustment, thus having measures comparable to IQ scores from WAIS. Then, an exploratory analysis on the nine subscales of PAS was performed, and a principal-component analysis (PCA) was run. The Kaiser-Mayer-Olkin measure for the sampling adequacy and Bartlett's test of sphericity were calculated. Scree-plot and Kaiser's criterion were used to extract principal factors. We used orthogonal rotation to discriminate between factors and then we calculated Cronbach's alpha to check the reliability of the scales. Then, IQ was standardized in z-scores, in order to obtain mean 0 and standard deviation 1 for each of the scales. Secondly, PAS was also stratified by age-range (i.e. <12 years and between 12-16 years) and another PCA with the same abovementioned criterions was performed, for the purpose of the exploratory analyses.

8. Statistical analysis

To compare socio-demographic, cognitive, premorbid characteristics and pattern of cannabis use between case and control group a univariate analysis was performed using t-test or Welch test for quantitative variables and Pearson 2 test for qualitative variables. The latter test was also used to compere clinical characteristics (i.e. diagnoses) in case group. Bivariate correlations between IQ and PAF and PSF scores were controlled by using Pearson's Test.

To study the possible aggregation of categories of level of education, relationship status, occupational status, living status and frequency of cannabis use, logistic regressions were computed using group as dependent variable in order to predict which groups (case or control) a person is likely to belong to given certain information.

To compare the main effects and interaction terms of lifetime cannabis use (yes or no) and group belonging (cases or controls) on Premorbid Social Factor (PSF), Premorbid Academic Factor (PAF) and IQ scores, I used 3 ANCOVA models. "Country" was included in the model as fixed factor and the model was adjusted by age, gender and ethnicity and, additionally, by occupation and education for IQ.

To compare the main effects and the interactions terms of cannabis use, by frequency (never, less frequently than everyday and everyday) and group (case or controls) on IQ, premorbid social and academic adjustment scores a MANOVA with these three outcomes (manipulated as abovementioned) was performed, controlled for sociodemographic main variables (i.e. age, gender, ethnicity) and country. Box's M resulted significant but this test is highly sensitive. Because we can consider equal sample sizes, heterogeneity is not an issue (Tabachnick & Fidell, 2001).

Moreover, I wanted to use a MIXED ANCOVA model to study the difference on PAF and PSF between the two ranges of age (i.e. time before 12 years and between 12 and 16 years) controlling for gender, ethnicity and country.

I used group (case or control), time of PAS (12 or 16 years) and frequency of cannabis use as independent variables and a casual effect for id-patient to take into account the repeated measures (12 or 16 years) for each patient.

To study the main effect and interaction terms of diagnosis and frequency of cannabis use on IQ, an ANCOVA model was fitted controlling for gender, age and ethnicity on patients' group only.

A multinomial regression was used in order to compare the risk to everyday user or less than everyday user, rather than never users, taking into account WAIS subscales, PAF and PSF as predictors, along with other variables. This analysis was preferred, instead of an ordered logistic regression, because it permits a comparison between all categories (i.e. less than everyday vs never, everyday vs never and less than everyday vs everyday). Due to the large number of potential interactions among indipendent varaibles in both analisys, it is not possible to estimate a saturated model and then I applied a backward and forward approach, where interactions of second and third order for each variable of interest were entered and then a F test was used to remove not significant variables. In order to look at other variables of interest in terms of different patterns of cannabis use (i.e. current use, age at first use, % of THC), a logistic regression was computed, using frequency of cannabis use as an outcome variable to estimate the risk to be everyday user or less than everyday user, taking into account a list of predictors.

The assumption of normality of the data that underlies statistical parametric approach is considered verified because a large sample is used, as suggested in the central limit theorem. P-values <0.05 were considered statistically significant and further corrected by Bonferroni.

9. Justification of sample size: power calculation

The EU-GEI study proposed a sample size for each Country. It used a hypothesised interaction between childhood abuse and the COMT genotype. The following assumptions were made: 1) a allele prevalence of 25% met/met, 50%

val/met and 25% val/val (based on Caspi et al., 2005); and 2) an overall prevalence of abuse of 15% (based on May-Chahal & Cawson, 2005). In a restricted analysis of cases (n = 500) and siblings (n = 500), the study would have 99% power to detect the following interaction effect: a difference in proportions exposed to abuse between cases and controls of 0 in the met/met group (OR=1), of 0.15 in the val/met group (OR=2.4) and of 0.32 in the val/val group (OR=5.0). This is a smaller effect than that found by Caspi et al (2005) for adolescent cannabis use and COMT. This is illustrative and indicates high levels of statistical power to detect gene x environment effects in case-control analyses.

10. Ethics

In order to make sure that ethical issues would be dealt with appropriately, EU-GEI opted for the institution of a specific ethics work package. The goal of this work package is to continuously inspect and comment on ethical issues in EU-GEI, raise awareness and remedy any problems that might arise.

All core partners have to get ethical approval from their ethical committees prior to starting the research, e.g. the study was approved by the Ethical Committee of the Palermo University Medical School in 2010 and the data collection in the mental health services has been authorized by the Department of Mental Health of Palermo which is the coordinator of all the psychiatric services in the catchment area involved in the study.

During recruitment, the subjects received background information on the study and signed their consent. An important first step in the study was confirming that the potential participants were capable of making an informed decision. Subjects were explicitly told that they could stop at any time without consequences. Data (genetic variation, environmental exposures, clinical and demographic measures, patient status) were stored anonymously.

In principle, all projects follow the guideline “Ethics for researchers” ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethics-forresearchers.pdf.

The ethics work package will see to it that research is conduced in accordance with the following sources:

- UNESCO International Declaration on Human Genetic Data. 2003;
- UNESCO Universal Declaration on Bioethics and Human Rights. 2005;
- EU Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data;
- EU Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;
- Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.1997;
- Council of Europe. Recommendation Rec (2006) on research on biological materials of human origin;
- Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research. 2005;
- Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes. 2008.

Previously collected data that have been used in EU-GEI have undergone the required evaluation by local ethics committees and obtained all the required permissions (e.g. SGAP and GAP study).

Data protection includes the strict separation of information identifying the subjects, such as name, address, site of residence, from the diagnostics, determinants or outcomes. Human data have been stored in a separate locked compartment, which is accessible only for staff working on the project and the local

investigator. All staff working on the project have to sign confidentiality documents before getting access to human data.

11. Statment of contribution to the investigations

My work has been inspired and guided by my supervisors: Prof. Daniele La Barbera, Prof. Robin Murray and Prof. Marta Di Forti who gave me the opportunity to be involved in the GAP and SGAP studies first and in the EU-GEI study from its start. I have been actively involved in the recruitment of both cases and controls and in the participants' assessment and in the retrospective study on clinical notes.

I was part of the Sicilian Genetic and Psychosis study (S-GAP) and EU-GEI research team of psychologists and psychiatrists in training who performed the screening in the mental health services together with me from the start to the conclusion (i.e. from 2008). I carried out the clinical assessment on a large proportion of the cases and controls recruited in Palermo, especially for the neuropsychological part of the assessment (including WAIS). In 2011, I spent one year in the GAP study, at the Department of Psychosis Studies (King's College – London), where I helped with data screening, collecting and analyzing for the pilot study described in Chapter 4. I first started at King's my involvment in EU-GEI project, taking part at the assessment of some patients and controls for the neuropsychological battery, after a training with Prof. Craig Morgan.

In 2016 I had again the opportunuty to spend a period of few months at the Department of Psychosis Studies, being involved in data cleaning and project's initial database and where I could write this work of thesis, supervised by Prof. Robin Murray and Prof. Jim Van Os. During this period of time, I was also in charge for the data cleaning-up for WAIS, PAS and some MRC variables for the entire database (e.g. data from all Countries).

I finally organised the project's initial database in (SPSS 22) and I built the variables relevant to my thesis, to perform the analyses.

My work was only a little part of a greater and hard working team, without whom I would not have been able to develop the present project.

Chapter 4

Pilot study

1. Introduction

In this chapter I am going to describe the pilot study, conducted in 2011 at King's College on a sample collected as part of the GAP study.

This section of the Thesis is adapted from the paper published in Schizophrenia Research in 2013, with the title "*Cannabis users have higher premorbid IQ than other patients with first onset psychosis*", thanks to the supervision of Prof. Robin Murray and Prof. Marta Di forti and the following co-authorship: Laura Ferraro, Manuela Russo, Jennifer O'Connor, Benjamin D.R. Wiffen, Maria Aurora Falcone, Lucia Sideli, PoonamGardner-Sood, Simona Stilo, Antonella Trotta, Paola Dazzan, Valeria Mondelli, Heather Taylor, Bess Friedman, Hannah Sallis, Caterina La Cascia, Daniele La Barbera, Anthony S. David, Abraham Reichenberg, Robin M. Murray and Marta Di Forti (Ferraro et al., 2013, see **Appendix VI**).

2. Aims and Hypotheses

We set out this study to test the hypothesis that patients who have smoked cannabis show a higher premorbid IQ compared to those who did not in a representative group of FEP patients, including those with affective psychosis, and a matched control group, whilst controlling for important social and demographic

variables. We did not expect to find any such relationship between cannabis use IQ and premorbid IQ in controls.

3. Methods

3.1. Sample

Our data were derived from the Genetics and Psychosis (GAP) study (Aas et al., 2011; Di Forti et al., 2009, 2012; Mondelli et al., 2010; O'Connor et al., 2012) a case–control study of first-episode psychosis, conducted in consenting patients aged 18–65 years admitted to *the South London and Maudsley Mental Health NHS Foundation Trust* (SLaM). This study was supported by the UK National Institute of Health Research Biomedical Research Centre grant (NIHR-BRC, SLAM) and Palermo University (Italy) founded my Research Felloship.

We collected data on cannabis consumption and neuropsychological performance from 279 subjects (119 patients and 160 healthy controls). All subjects underwent an extensive assessment which included collecting information about their socio-demographic characteristics and lifetime substance use. Subjects were administered tests of premorbid (WTAR) and present intellectual level (WAIS-III), as soon as possible, based on their compliance and within the first six months after their admission.

3.1.1. Patients

119 patients met ICD-10 criteria for psychosis (F10–19, F20–F29 and F30–F33) (World Health Organization, 1992); 33 of them had a diagnosis of affective psychosis, while 86 were diagnosed as non-affective psychosis. Exclusion criteria were applied as follows: organic psychosis, acute intoxication (F1x.0), learning disabilities, history of traumatic brain injury and lack of English fluency.

3.1.2. Controls

Healthy controls were recruited from the same catchment area as the patients, through local newspapers and internet advertising, job centers, hospitals and a pre-existing volunteer database. They were representative of the general population in age, gender, ethnicity and employment status (Di Forti et al., 2009) and the *Psychosis Screening Questionnaire* (PSQ) (Bebbington & Nayani, 1995) was administered to exclude subjects who had any psychotic symptomatology.

3.2. Assessment

A modified version of the *Medical Research Council* (MRC) *Sociodemographic Schedule* (Di Forti et al., 2009) was administered to all subjects. Ethnicity was self-ascribed during the interview and grouped into "white", "black" and "other".

Diagnoses for patients were established using the *Operational Criteria Checklists* (OPCRIT) (McGuffin et al., 1991). Levels of positive and negative symptoms were assessed by administering *the Positive and Negative Syndrome Scale* (PANSS), thus deriving scores for positive, negative and general symptoms (Kay, Opler, & Lindenmayer, 1989). By using the *Cannabis Experience Questionnaire* (modified version) (Di Forti et al., 2009), all subjects were assessed for lifetime cannabis use (used at least once), age at first use in years (then dichotomized according to mean age at first use), type of cannabis used most often (hash/imported herbal cannabis or – alternatively – skunk, high potency cannabis), frequency of use (everyday/less frequently), current use (customarily smoking cannabis/no), mode of use (social/isolated), self-estimated number of times that they used cannabis over the lifetime (operationalized as described in **Table 8**) and lifetime use of other drugs (yes/no). Current IQ was estimated based on five subtests (Information, Digit Span, Matrix, Block Design and Digit Symbol) of the *Wechsler Adult Intelligence Scale—Third Edition* (WAIS-III) (Wechsler, 1997). Premorbid IQ was estimated using the *Wechsler Test of Adult Reading* (WTAR), a reading test normed with the WAIS-III, which is able to provide a broad estimate of general ability before the illness (Holdnack, 2001).

3.3. Statistical analyses

Chi-square ($\chi 2$) tests and t-tests were used where appropriate to compare socio-demographic characteristics between cases and controls. Equality of variance was tested using Levene's test. A significance level of 5% (two-tailed) was initially specified; this was adjusted using a Bonferroni correction in the analysis of covariance (ANCOVA).

Estimated current IQ (WAIS) and premorbid IQ (WTAR) scores were compared between the groups, first using a t-test and then using ANCOVA to adjust for confounders in order to check if cases were lower in IQ and premorbid IQ than controls. Potential confounders were selected *a priori* based on the literature.

In order to avoid overfitting the model, significance tests (Pearson correlations, t-tests and chi-squared tests) were used to select which of these to include in the ANCOVA. These included: gender, mother tongue, ethnicity and years of education (years attended school). Next, we stratified by group and used an independent two-tailed t-test to compare mean IQ and premorbid IQ between people with any lifetime cannabis use and those without, and also between different patterns of cannabis use (**Table 8**).

This analysis was carried out in order to test the specific hypothesis that patients with lifetime cannabis use were better in their premorbid IQ. A 2 factorial ANCOVA was run (groups [cases, controls] x cannabis [cannabis yes, cannabis no]) controlling for covariates as specified previously; the inclusion of a cannabis by group interaction term formally tested whether the relationship between cannabis and IQ and premorbid IQ differed in cases and controls. Finally, a score measuring the difference between current IQ and premorbid IQ (current IQ minus premorbid IQ) was calculated for the patient group only. We then carried out an ANCOVA using this score as the dependent variable and lifetime cannabis use [yes, no] as fixed factor, whilst additionally controlling for years of education and mother tongue (dichotomized as English vs. Not English first language), which a preparatory analysis showed to be related to differences between IQ and premorbid IQ. This analysis tested the hypothesis of a smaller difference between IQ and

premorbid IQ in patients with cannabis use, compared with patients without any use of cannabis. Statistical analyses were carried out using SPSS 15.0 for Windows (SPSS, 1994).

4. Results

4.1. Socio-demographic characteristics

Table 7 shows socio-demographic characteristics of patients and controls. There were no differences in mean age at assessment between cases and controls. Statistically significant differences emerged between patients and controls in gender (higher percentage of males in cases than in controls), ethnicity (higher percentage of black and other ethnic minority groups among cases) and years of education (fewer years of education among cases). The case group also contained a greater percentage of unemployed people at the time of assessment. All of these differences were expected (see also Di Forti et al., 2009) and, therefore, used as covariates.

Table 7. Socio-demographic characteristics (Pylot Study).

	Cases	N	Controls	N	*t*-test or χ^2	df	p
Age in years, mean (s.d.)	29.6 (8.5)	119	29.6 (10.8)	160	0.03	277	.971
Males, n (%)	84 (70.6)	119	83 (51.9)	160	9.9	1	**.002**
Ethnicity, n (%)		111		159	16.8	2	**<.001**
White	33 (29.7)		95 (59.7)				
Black	55 (49.5)		47 (29.6)				
Other	23 (20.7)		17 (10.7)				
English mother tongue, n (%)	86 (72.3)	117	133 (83.1)	160	4.7	1	.052
Years of education, mean (s.d.)	13.2 (3.7)	108	15.1 (2.9)	147	4.1	200.1	**<.001**
Unemployed, n (%)	63 (59.4)	106	27 (22.0)	123	33.5	1	**<.001**

Abbreviation: df=degree of freedom.

4.2. Pattern of cannabis use

Table 8 reports patterns of cannabis use by group. All patients who reported use of cannabis in their lifetime started using cannabis prior to the onset of psychosis.

Table 8. Patterns of Cannabis Use by Group (Pylot Study).

	Cases	N	Controls	N	*t*-test or χ^2	df	p
Ever used cannabis lifetime, n (%)	86 (72.3)	119	98 (62.0)	158	3.1	1	.074
Age in years of first use of cannabis[a], mean (s.d.)	16.4 (4.6)	82	16.1 (3.0)	98	0.70	135.5	.498
Current cannabis users[a], n (%)	34 (39.1)	87	36 (36.4)	99	0.1	1	.703
Frequency of use (everyday/less frequently)[a], n (%)	38 (48.7)	78	15 (17.0)	88	19.08	1	**<.001**
Type of cannabis used[a], n (%)		66		86	−4.59	1	**.045**
Hash and imported herbal cannabis	23 (34.8)		44 (52.4)				
Sinsemilla (skunk)	43 (65.2)		42 (28.8)				
Mode of cannabis use[a], n (%)		77		92	1.65	2	.437
Socially	49 (63.6)		67 (72.8)				
Isolated	13 (16.9)		12 (13.0)				
Both	15 (19.5)		13 (14.1)				
Number of times of cannabis use lifetime[a], n (%)		60		88	1.29	3	.730
Once or twice only–fewer than 10 times	12 (20.0)		14 (15.9)				
Between 10 and 50	3 (5.0)		7 (7.9)				
Between 50 and 200	9 (15.0)		10 (11.4)				
Over 200 times	36 (60.0)		57 (64.8)				
Ever used other illicit drugs lifetime, n (%)	51 (45.1)	113	53 (34.6)	153	3.0	1	.083
Drugs use (general), n (%)		119		158	4.66	2	.187
No drugs	33 (27.7)		60 (38.0)				
Only cannabis	37 (31.1)		45 (38.5)				
Cannabis and other drugs	49 (41.2)		53 (33.5)				

Abbreviation: df = degree of freedom. [a] In those who had ever used cannabis. Ferraro et al. 2013

There were no significant differences in ever having used cannabis or other illicit drugs between cases and controls. Among those who had used cannabis, there were no significant differences between cases and controls in age of first use, current cannabis use, context of use (isolated or social), or the number of times that they had used cannabis. Statistically significant differences between cases and controls were, however, found in the type and the frequency of cannabis used.

Cases were more likely than controls to have preferentially smoked "skunk" which has a relatively high concentration of Δ9-THC (12–18%) (Potter, Clark, & Brown, 2008), and were more likely to have used cannabis everyday than controls. There were no significant differences between cases who used cannabis and those who did not in gender, age, ethnicity, years of education, mother tongue nor in any of the PANSS subscales: negative ($t(111) = -1.187$, $p = .238$), positive ($t(111) = .677$, $p = .500$) and general psychopathology ($t(111) = -.386$, $p = .700$) scores (data not shown in tables).

4.3. Current IQ and premorbid IQ in cases and controls

Differences between cases and controls emerged in terms of current IQ ($t(247) = 8.99$, $p < 0.001$) and premorbid IQ ($t(181) = 10.81$, $p < 0.001$). Cases had a mean current IQ of 87.9 (16.2) and controls of 106.6 (16.2); cases had a mean premorbid IQ of 91.2 (11.3) compared with 102.0 (10.5) in controls.

ANCOVAs were subsequently carried out adjusting for gender, years of education, mother tongue and ethnicity. Age was not included since WAIS scores and WTAR already take this into account. After adjusting for the above covariates, patients still performed significantly worse than controls in IQ ($F(1,233) = 53.1$, adjusted $p < 0.001$, $\eta^2 = 0.186$) and premorbid IQ ($F(1,169) = 27.0$, adjusted $p < 0.001$, $\eta^2 = 0.138$).

4.4. Association of IQ and premorbid IQ with cannabis use when stratifying by case/control groups

In cases, IQ ($t(104) = 3.6$, $p < 0.001$) and premorbid IQ ($t(81) = 2.9$, $p = 0.004$) were significantly higher among patients who had used cannabis compared with those who had never used it (**Table 9**). In contrast, in the controls there were no statistically significant differences either in IQ ($t(141) = -0.2$, $p = 0.757$) or in premorbid IQ ($t(98) = 0.6$, $p = 0.156$) scores between those who did or did not use cannabis.

ANCOVAs adjusting for gender, education, mother tongue and ethnicity, still gave similar results in the case group for both IQ ($F(1,86) = 21.6$, adjusted $p < 0.001$, $\eta^2 = 0.201$) and premorbid IQ ($F(1,66) = 10.6$, adjusted $p = 0.002$, $\eta^2 = 0.139$) (not shown in table). We did not find any such significant differences when analysing the control group (all $p > 0.05$).

Table 9. Comparing IQ and premorbid IQ across different patterns of cannabis use (Pylot Study).

	Cases			Controls		
	Mean (s.d.)	Mean (s.d.)	p	Mean (s.d.)	Mean (s.d.)	p
Cannabis use lifetime (yes/no)						
IQ	93.3 (11.0)	85.5 (10.1)	**<.001**	106.3 (15.1)	106.9 (17.9)	.838
Premorbid-IQ	91.2 (16.5)	79.1 (11.5)	**.004**	102.5 (10.2)	101.0 (10.9)	.518
Current use[a] (yes/no)						
IQ	91.6 (12.8)	90.6 (18.5)	.796	103.6 (17.5)	107.5 (13.4)	.223
Premorbid-IQ	91.6 (11.1)	94.7 (10.7)	.285	101.6 (10.7)	102.7 (10.1)	.659
Type of cannabis[a] (skunk/hash)						
IQ	88.8 (13.3)	93.0 (16.8)	.310	107.8 (16.0)	103.2 (13.9)	.118
Premorbid-IQ	93.2 (9.9)	92.8 (12.8)	.922	105.0 (9.2)	99.0 (11.9)	.069
Age first use in years[a] (>16/≤16)						
IQ	87.1 (15.3)	93.0 (17.3)	.154	112.3 (16.1)	103.8 (14.0)	**.016**
Premorbid-IQ	89.8 (10.2)	95.4 (11.4)	.075	104.7 (10.3)	101.3 (10.1)	.216
Mode of use[a] (alone/social)						
IQ	89.0 (9.5)	90.7 (17.2)	.745	105.0 (21.9)	107.0 (14.0)	.696
Premorbid-IQ	89.5 (10.0)	94.8 (11.3)	.172	101.3 (11.8)	102.4 (9.5)	.759
Frequency[a] (everyday/less freq)						
IQ	88.5 (14.3)	94.9 (16.1)	.086	109.1 (16.1)	105.1 (15.0)	.378
Premorbid-IQ	92.2 (11.9)	94.6 (10.5)	.582	101.5 (12.4)	102.3 (9.4)	.805
N. of times[a] (over/under 200 times)						
IQ	88.2 (14.6)	86.5 (16.7)	.691	106.8 (16.6)	103.3 (15.5)	.358
Premorbid-IQ	89.9 (10.6)	90.2 (12.2)	.925	103.5 (10.3)	101.0 (10.7)	.427

[a] In those who had ever used cannabis.
Ferraro et al., 2013.

4.5. Patterns of cannabis use and IQ

T-tests in the group of lifetime cannabis users were only performed to establish whether current cannabis use, type of cannabis used, frequency of use, mode of use, number of times used or age at first use were associated with IQ or premorbid IQ. None of these variables were found to have a significant association with either IQ or premorbid IQ among cases or controls (all $p > 0.05$). We only found that controls who had smoked cannabis after age 16, had higher IQ than controls that had smoked cannabis earlier in life ($p = 0.016$) (see also Meier et al., 2012) (**Table 9**).

4.6. IQ and premorbid IQ scores association with cannabis use: Case–control comparisons

4.6.1. IQ

Factorial ANCOVA confirmed a significant main effect of the group (case/control) on IQ scores ($F(1,222) = 53.3$, $p < 0.001$, $\eta^2 = 0.205$). There was also a significant main effect of cannabis use ($F(1,222) = 8.1$, $p = 0.005$, $\eta^2 = 0.036$). The interaction effect between cannabis use and the group was significant ($F(1,222) = 13.7$, $p < 0.001$, $\eta^2 = 0.058$), indicating that the IQ of cases and controls

was related differently to cannabis use. Specifically, the IQ of patients was significantly related to cannabis use ($F(1,86) = 21.6$, $p < 0.001$, $\eta^2 = 0.201$), whilst the IQ of the controls was not ($F(1,132) = 0.7$, $p = 0.399$).

4.6.2. Premorbid IQ

A factorial ANCOVA showed a significant main effect of the group (case/control) on premorbid IQ scores ($F(1,161) = 34.3$, $p < 0.001$, $\eta^2 = 0.176$), a main effect of cannabis ($F(1,161) = 6.2$, $p = 0.013$, $\eta^2 = 0.038$), and a significant interaction between cannabis and the group ($F(1,161) = 3.9$, $p = 0.048$, $\eta^2 = 0.024$) indicating that premorbid IQ of cases and controls was related differently to cannabis use. Whilst premorbid IQ of patients was significantly related to cannabis use ($F(1,66) = 10.6$, $p = 0.002$, $\eta^2 = 0.139$), premorbid IQ of the controls was not ($F(1,91) = 0.1$, $p = 0.730$).

4.6.3. Difference between IQ and premorbid IQ

A difference score was calculated (IQ minus premorbid IQ) for each of the patients. Those in the non-cannabis group were found to have a difference between premorbid IQ and IQ of 6.1 points greater (95% CI: 0.3, 11.7; $p = 0.037$) than that of patients who had used cannabis ($F(1,75) = 6.6$, adjusted $p = 0.012$, $\eta^2 = 0.081$). Diagnosis had no effect.

5. Discussion

The aim of this study was to test the hypothesis that among psychotic patients, those who had smoked cannabis would have a higher premorbid IQ than those who had not. Our main finding was in line with this hypothesis and showed that patients who had used cannabis in their lifetime had higher scores in both IQ and premorbid IQ compared to those patients who had never used cannabis.

5.1. Why is lifetime cannabis use associated with better premorbid IQ?

In our sample of cases, any lifetime use of cannabis was associated with a better premorbid cognitive performance, in line with reports by Yücel et al. (2012), Meijer et al. (2012), Rabin et al. (2013) and Schnell et al. (2012). Cognition has been established as a predictor of real world community functioning in schizophrenia (Green et al., 2000; Evans et al., 2003) and 69% of our sample of psychotic cannabis users reported a social use of cannabis, a similar proportion as in controls.

Thus, our findings are compatible with the view that, among psychotic patients, the better premorbid cognition of the group who had smoked cannabis is likely to have facilitated their use of the drug in a normal recreational way, sharing it with their friends. The findings are also compatible with the view that patients that used cannabis were less neurodevelopmentally impaired than those who did not. Other studies compatible with this latter view have reported that patients at their first episode who have used cannabis have fewer neurological soft signs signs (Ruiz-Veguilla, F. Callado, & Ferrin, 2012) and less abnormal MRI scans (Cunha et al., 2013) than those who have not.

5.2. Are IQ and premorbid IQ of patients and controls different in relation to cannabis use?

Looking at differences between cases and controls, we found, as expected, significantly lower current and premorbid IQ in patients on the overall. We also expected that cannabis use would be associated differently with IQ and premorbid IQ in patients and controls. Among cases, cannabis use was associated with a higher IQ and premorbid IQ, whilst among the controls, there was no significant difference. Previous studies compared cases and controls who used cannabis at age 16 or before and their performance in single tests: Jockers-Scherübl et al. (2007) found an interaction effect of group and cannabis on the “digit symbol” subtest from WAIS-R. Yücel et al. (2012) reported that “visual memory”, “working memory”, and “executive functioning” were better in patients who used cannabis, but no

interaction analysis was made with a corresponding control group. Meijer et al. (2012) found that lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition and face identity recognition, but they did not find any interaction effect with group status (patients, siblings and controls). To our knowledge, this is the first study that has investigated and found a relationship between IQ, premorbid IQ and cannabis use in cases but not in a comparison group of controls.

5.3. Difference between IQ and premorbid IQ in relation to cannabis use

As expected, the current IQ of patients was lower than their premorbid IQ on average (see also Dazzan et al., 2008). We calculated a difference score (IQ minus premorbid IQ) in order to see whether the estimated deterioration was associated with cannabis use (see also Leeson, Harrison, et al., 2011), and found this to be the case. This raises the possibility of a neuroprotective action of cannabis. However, those who used cannabis daily were neither less, nor more impaired than less frequent users; this was also the case when we compared patients that had started smoking cannabis at 16 or earlier (our mean age for cannabis use onset — the lowest age of first use in our sample was 5 years), and also when we compared patients that had smoked cannabis more or less than 200 times in their life, or patients that were currently smoking cannabis or not. Thus, we cannot make a definite statement on the question of any protective effect of cannabis use.

4.4. Limitations and strengths

We examined patients at their first episode of psychosis, which minimizes the influence from variables inherent to those with chronic illness and/or the effects of continuous pharmacological treatment on cognition. However, patients were not medication naïve and, as is well known, medication could have affected current neuropsychological performance (i.e. IQ) even in the short period between initial contact with the services and our cognitive testing. On the other hand, as already

mentioned, WTAR – our main measure of interest – is also robust in patients exerting suboptimal effort due to medication effects.

The inclusion of a control group was another strength of our study, but, as some demographic differences show, our strategy of recruiting controls representative of the local population could have biased our findings. However, we corrected our analysis for these characteristics and differences in neuropsychological performances stayed significant. Otherwise, as already discussed in Di Forti et al. (2009), it seems unlikely that the difference in frequency and type of cannabis used between cases and control group was driven by a recruitment bias. Cannabis use was self-reported but we measured the reliability of the self-reported data on current users in a random sample of 56 cases from the GAP sample, by carrying out a urinary drug screening (UDS).

Of the 56 cases tested, 34 had reported they were not current users; 32 of these (88%) had a negative UDS, only 2 tested positive. Thus, the accuracy of self-report data on current use in our sample is high. For obvious reasons, a history of lifetimeuse of cannabis cannot be assessed by a biological test. Finally, we are aware that reading-based tests have some limitations as a measure of premorbid IQ (O'Connor et al., 2012; Russell et al., 2000). However, WTAR is thought to be a more reliable measure of pre-morbid IQ (R. E. A. Green et al., 2008) compared to other tests like the NART (*National Adult Reading Test*) (Nelson and Willison, 1991) and is able to indicate a "hold" intellectual capacity (Horn & Cattell, 1966).

6. Conclusions

Our findings are in line with the hypothesis that among psychotic patients, cannabis users had a higher premorbid IQ than non-users (an association not witnessed among controls). Our cannabis-using patients also had a smaller difference between current IQ and premorbid IQ than non-using patients. Kremen et al., (2008) point out that premorbid estimates should be understood as a measure of "potential" had a given subject not been destined to develop schizophrenia. Thus,

individuals with a high premorbid IQ could be seen as less predisposed. Taking these findings together with the substantial evidence that cannabis use is a risk factor for psychosis, we suggested in this study that cannabis may play a role in provoking psychosis in people who were less neurodevelopmentally impaired than is generally the case in psychosis.

Chapter 5

Results

1. Introduction

In this section I am going to summarize the results of the study. In the first part I will be described the sample and its distribution by Country, socio-demographic characteristics, cognitive and premorbid characteristics, pattern of cannabis-use, other drug-use and clinical characteristics of case group. In the second part, I will describe the Principal Component Analysis for PAS factors and other data manipulations and in the third part I will show the progression of the model by frequency of cannabis use. The last part of the chapter will be dedicated to further exploratory analyses.

2. Descriptive Characteristics

2.1. Sample Characteristics

Across all sites, 1,168 cases were assessed in detail and form the case sample for case-control analyses. Across all sites 1,855 controls were recruited and assessed. Patients recruited were those who accepted to be enrolled, while patients who weren't involved in the study, either because they refused to be interviewed or because they had been screened and identified retrospectively by the leakage study, were entered as part of the incidence sample (1,338 psychotic subjects).

Complete case analysis deletes all units with incomplete data and the final sample of the present study therefore included 1,895 subjects (834 cases and 1,061 controls), with complete information about cannabis use (CEQ) and premorbid adjustment (PAS) at least, distributed by site and Country as described in **Table 10**.

Table 10. Sample Distribution by Site and Country.

Country	Cases	Controls	TOT, %
United Kingdom	**215**	**345**	**560 (29.5)**
London	173	239	412
Cambridge	42	106	148
Holland	**193**	**220**	**413 (21.8)**
Amsterdam	94	104	198
Leiden	99	116	215
Spain	**202**	**217**	**419 (22.1)**
Madrid	60	76	136
Barcelona	29	37	66
Oviedo	39	35	74
Valencia	49	32	81
Galicia	25	37	62
France	**102**	**144**	**246 (13.0)**
Paris	87	99	186
Puy de Dome	15	45	60
Italy	**122**	**135**	**257 (13.6)**
Palermo	56	94	150
Bologna	66	41	107
TOTAL	**834**	**1,061**	**1,895 (100)**

2.2. Socio-Demographic Characteristics

The most relevant socio-demographic characteristics of the sample by cases and control status are described in the next tables.

As expected, the case group shows a greater percentage of males (63.1%) compared to control group ($p<0.001$). Cases are generally younger than controls ($p<0.001$) and include a greater percentage of black and people of other ethnicity than controls ($p<0.001$) (**Table 11**).

Table 11. Socio-demographic Characteristics of the Sample by Cases and Controls.

Variables	Cases	N	Controls	N	χ2 or t-test	df	*p-value*
Gender		**834**		**1,061**	**45.6**	**1**	**<0.001**
Male, N (%)	526 (63.1)		504 (47.5)				
Female, N (%)	308 (36.9)		557 (52.5)				
Age, Mean (SD)	30.2 (10.4)	**833**	36.7 (13.3)	**1,059**	**11.8**	**1,890**	**<0.001**
Ethnicity		**831**		**1,050**	**54.5**	**2**	**<0.001**
White, N (%)	536 (64.5)		837 (79.7)				
Black, N (%)	141 (17.0)		104 (9.9)				
Other, N (%)	154 (18.5)		109 (10.4)				

Legend: SD=standard deviation; df=degree of freedom.

Controls have more years of education (p<0.001) and they achieved higher levels of education than cases (p<0.001). Cases are more likely to be unemployed than controls (p<0.001) at the moment of the interview (**Table 12**) as well as 5 years before (p<0.001) (data not shown in table).

Table 12. Characteristics of the Sample by Cases and Controls: Education and Work.

Variables	Cases	N	Controls	N	χ2 or t-test	df	*p-value*
Education		**832**		**1,061**	**200.9**	**5**	**<0.001**
No qualification, N (%)	113 (13.6)		30 (2.8)				
Compulsory education, N (%)	217 (26.1)		142 (13.4)				
1st level non-compulsory, N (%)	183 (22.0)		247 (23.3)				
Job-related education, N (%)	173 (20.8)		205 (19.3)				
University 1st degree, N (%)	100 (12.0)		250 (23.6)				
University degree, (N, %)	46 (5.5)		187 (17.6)				
Years of education, Mean (SD)	13.5 (3.9)	**830**	15.4 (3.8)	**1,061**	**10.6**	**1,889**	**<0.001**
Occupational status		**819**		**1,012**	**220.1**	**5**	**<0.001**
Unemployed, N (%)	324 (39.6)		153 (15.1)				
Economically inactive, N (%)	145 (17.7)		107 (10.6)				
Student, N (%)	123 (15.0)		169 (16.7)				
Part-time employee, N (%)	72 (8.8)		142 (14.0)				
Full-time employee, N (%)	123 (15.0)		382 (37.7)				
Self-employed, N (%)	32 (3.9)		59 (5.8)				

Legend: SD=standard deviation; df=degree of freedom.

With respect to the relationship and living status, cases are more likely to be single and to not ever have had a long-term – more than 1 year – relationship in their lifetime than controls (all p<0.001). They are also less likely to have lived alone than controls (p<0.001), probably because they are still living with their parents more frequently than controls (p<0.001) (**Table 13**).

At this point it is important to remember that the control group was selected to be representative of the general population of each area and not to be matched with the case group.

Table 13. Characteristics of the Sample by Cases and Controls: Relationship and Living Status.

Variables	Cases	N	Controls	N	χ2	df	*p-value*
Relationship status		**822**		**1,011**	**262.3**	**4**	**<0.001**
Single N (%)	551 (67.0)		313 (31.0)				
Married, living together, N (%)	127 (15.5)		426 (42.1)				
In a steady relationship, N (%)	92 (11.2)		216 (21.4)				
Divorced, separated, N (%)	48 (5.8)		47 (4.6)				
Widowed, N (%)	4 (0.5)		9 (0.9)				
Long-term relationship lifetime		**815**		**1,011**	**122.8**	**1**	**<0.001**
Yes, N (%)	529 (64.9)		878 (86.8)				
No, N (%)	286 (35.1)		133 (13.2)				
Living status		**818**		**1,010**	**246,5**	**7**	**<0.001**
Alone, N (%)	139 (17.0)		159 (15.7)				
Alone, with children, N (%)	31 (3.8)		48 (4.8)				
Partner, N (%)	70 (8.6)		219 (21.7)				
Partner, with children, N (%)	77 (9.4)		267 (26.4)				
Parents, N (%)	336 (41.0)		187 (18.5)				
Other family, N (%)	64 (7.8)		19 (1.9)				
Friends, N (%)	40 (4.9)		68 (6.7)				
Other (e.g. hostels, hall of residence), N (%)	61(7.5)		43 (4.3)				
Since leaving your parent's home, have you lived with others?		**746**		**959**	**55.5**	**1**	**<0.001**
Yes, N (%)	495 (66.4)		787 (82.1)				
No, N (%)	251 (33.6)		172 (17.9)				

Legend: SD=standard deviation; df=degree of freedom.

2.3. Cognitive Characteristics

Across all sites, 705 cases and 1,034 controls were assessed with WAIS, in order to obtain four scaled scores (Ss) to estimate the IQ, as it is showed in **Table 14**, 8.2% of the sample was missing for these values.

As expected, patients performed worse than controls in all cognitive domains and in general IQ (all p<0.001) and these differences stayed significant even after controlling for gender, ethnicity and level of education (all p<0.001). Age was not used as covariate because it is already taken into account in IQ calculation.

Table 14. Cognitive Characteristics of the Sample by Cases and Controls from WAIS Scores.

Variables	Cases	N	Controls	N	t-test	df	*p-value*	Adj *p-value**
Digit Symbol - Ss		**708**		**1,034**	**25.4**	**1,740**	**<0.001**	**<0.001**
Mean (SD)	6.6 (3.0)		10.4 (3.1)					
Arithmetic - Ss		**707**		**1,039**	**13.4**	**1,744**	**<0.001**	**<0.001**
Mean (SD)	7.7 (3.5)		10.0 (3.5)					
Block Design - Ss		**705**		**1,037**	**14.3**	**1,740**	**<0.001**	**<0.001**
Mean (SD)	7.6 (3.8)		10.3 (3.7)					
Information - Ss		**706**		**1,039**	**9.9**	**1,743**	**<0.001**	**<0.001**
Mean (SD)	8.9 (4.0)		10.8 (3.7)					
Total IQ		**705**		**1,034**	**20.2**	**1,737**	**<0.001**	**<0.001**
Mean (SD)	84.5 (19.2)		103.9 (18.5)					

Legend: Ss= Scaled scores; SD=standard deviation; df=degree of freedom;
* Adjusted for gender, ethnicity and level of education.

2.4. Premorbid characteristics

Across all sites, the differences between cases and controls in all the measures of premorbid adjustment were statistically significant (all p<0.001). Cases were less sociable, they had less peer relationships, they had a worse scholastic performance and a worse adaptation to school, both in childhood (<12 years) and in early adolescence (12-16 years). Cases were also more impaired in their socio-sexual aspects in early adolescence. All these differences remained significant after adjusting for age, gender and ethnicity (all p<0.001) (**Table 15**).

Table 15. Premorbid Characteristics of the Sample by Cases and Controls from PAS Scores.

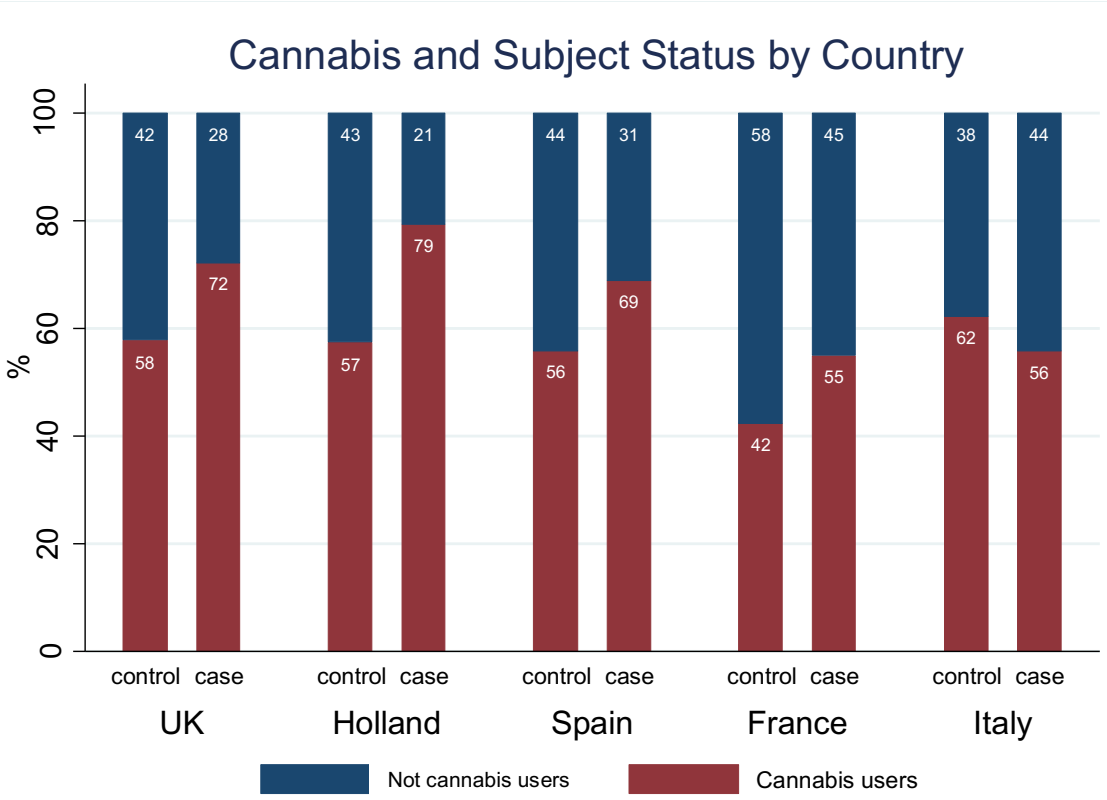
Variables	Cases	N	Controls	N	t-test	df	*p-value*	Adj *p-value**
1 –Sociability and withdrawal – Childhood (Soc<12), Mean (SD)	1.6 (1.5)	**834**	1.1 (1.3)	**1,061**	**-7.3 ****	**1,639**	**<0.001**	**<0.001**
2 – Sociability and withdrawal – Early Adolescence (Soc 16), Mean (SD)	1.7 (1.5)	**834**	1.1 (1.2)	**1,061**	**-9.7 ****	**1,574**	**<0.001**	**<0.001**
3 –Peer Relationships – Childhood (Peer<12), Mean (SD)	1.6 (1.3)	**832**	1.1 (1.1)	**1,061**	**-9.1 ****	**1,641**	**<0.001**	**<0.001**
4 –Peer Relationships – Early Adolescence, (Peer 16), Mean (SD)	1.7 (1.4)	**833**	0.1 (1.1)	**1,061**	**-12.3 ****	**1,581**	**<0.001**	**<0.001**
5 –Scholastic Performance – Childhood (Schol<12), Mean (SD)	2.7 (1.5)	**830**	1.9 (1.4)	**1,061**	**-11.6 ****	**1,715**	**<0.001**	**<0.001**
6 –Scholastic Performance – Early Adolescence (Schol 16), Mean (SD)	3.2 (1.5)	**822**	2.2 (1.5)	**1,056**	**-13.7**	**1,876**	**<0.001**	**<0.001**
7 –Adaptation to School – Childhood, (Adap<12), Mean (SD)	1.3 (1.3)	**831**	0.6 (0.9)	**1,061**	**-12.3 ****	**1,459**	**<0.001**	**<0.001**
8 –Adaptation to School – Early Adolescence, (Adap 16), Mean (SD)	1.9 (1.5)	**821**	1.1 (1.3)	**1,056**	**-12.6 ****	**1,611**	**<0.001**	**<0.001**
9 –Socio-Sexual Aspects During Early Adolescence, (Sex 16), Mean (SD)	1.1 (1.5)	**828**	0.8 (1.2)	**1,059**	**-5.4 ****	**1,544**	**<0.001**	**<0.001**

Legend: SD=standard deviation; df=degree of freedom;
* Adjusted for gender, age, ethnicity and level of education; **Levene's test <0.05.

2.5. Pattern of Cannabis Use

Figure 13 shows the distribution of cannabis use across different countries. Holland and UK have the higher percentages of cannabis smokers in case group and overall, compared to other countries.

Figure 13. Distribution of Cannabis Use Across Different Countries.



Legend: this histogram displays on the Y axis the percentages of cases and controls who smoked cannabis in their lifetime (in red) distributed by country.

Table 16 shows some aspects of pattern of cannabis use, by comparing them between cases and controls. Cases were more likely to have used cannabis in their lifetime ($p<0.001$) and to currently use cannabis ($p<0.001$). Among cases who smoked cannabis, a greater percentage of them used cannabis everyday ($p<0.001$) and they started the consumption at an earlier age, compared to controls ($p<0.001$). More cases than controls declared that they had increased the amount of cannabis used due to tolerance induced by the substance (<0.001).

Table 16. Pattern of Cannabis Use of the Sample by Cases and Controls from CEQ.

Variables	Cases	N	Controls	N	t-test or $\chi 2$	df	*p-value*
Cannabis Use Lifetime		**834**		**1,061**	**32.1**	**1**	**<0.001**
Yes, N (%)	571 (68.4)		591(55.7)				
No, N (%)	263 (31.5)		470 (44.3)				
Current Cannabis Use		**830**		**1,059**	**38.0**	**1**	**<0.001**
Yes, N (%)	202 (24.3)		141 (13.3)				
No, N, (%)	628 (75.7)		918 (86.7)				
Age at First Use		**565**		**591**	**-3.5**	**1,154**	**<0.001**
(mean, SD)**	16.9 (4.7)		17.8 (4.5)				
Frequency of use**		**563**		**589**	**161.5**	**4**	**<0.001**
Everyday, N (%)	256 (45.5)		81 (13.8)				
(More than) once a week	96 (17.1)		89 (15.1)				
A few times each month	56 (9.9)		92 (15.6)				
A few times each year	58 (10.3)		108 (18.3)				
Only once or twice	97 (17.2)		219 (37.2)				
Tolerance increased amount**		**237**		**904**	**71.5**	**1**	**<0.001**
Yes, N (%)	173 (31.2)		64 (27.0)				
No, N, (%)	381 (68.8)		523 (89.1)				
Mode of use**		**528**		**571**	**80.9**	**1**	**<0.001**
Socially (N, %)	365 (69.1)		518 (90.7)				
On my Own (N, %)	163 (30.9)		53 (9.3)				
Type of cannabis used**		**514**		**545**	**23.3**	**1**	**<0.001**
Low-THC cannabis (N, %)	164 (34.2)		253 (46.4)				
High-THC cannabis (N, %)	350 (31.9)		292 (68.1)				
Cannabis is mostly used**		**535**		**560**	**3.8**	**4**	**0.422**
In a joint with tobacco (N, %)	488 (91.2)		492 (7.9)				
In a joint without tobacco (N, %)	26 (4.9)		41 (7.3)				
Using a bong (N, %)	8 (1.5)		9 (1.6)				
Ate or drank (N, %)	4 (0.7)		7 (1.3)				
Other (N,%)	9 (1.7)		11 (2.0)				

Legend: ** among those who used cannabis.

As is shown in **Table 16**, a greater percentage of cases (69.1%) and controls (90.7%) declared that they smoke cannabis socially, more than on their own, but this percentage was greater in controls than in cases ($p<0.001$). As expected, cases were also more likely to have used high potency cannabis, which means with total

levels of THC ≥10%. The Eu-GEI team, coordinated by Prof. Marta Di Forti, decided to initially establish this conservative cut-off of 10% THC concentration; if anything, this cut-off may underestimate the effect of high potency cannabis. There were no differences between cases and controls in the mode of cannabis use (p=0.422), cannabis was mostly used in a joint with tobacco.

Starting from data available from the European Monitoring Centre for Drugs and Drug Addiction and Europol (2016) and other reports (European Monitoring Centre for Drugs and Drug Addiction, 2016; European Monitoring Centre for Drugs and Drug Addiction - Ministerio de Sanidad Servicios Sociales e Igualidad, 2013; R. Niesink & Rigter, 2013; Observatoire Francais des Drogues et des Toxicomanies (OFDT), 2015; Potter et al., 2008), the distribution of cannabis use across all Countries was grouped as follows (**Table 17**).

Table 17. Distribution of drug use across all Countries according THC-absolute concentration.

Country	THC<10%	N (%)	THC≥10%	N (%)
United	Hash	108 (34.2)	Home-grown Skunk/Sensimilla	98 (31.0)
Kingdom	Imported herbal cannabis	78 (24.7)	Super skunk	23 (7.3)
	Geimporteerde Wiet	1 (0.3)		
		Unknown	8 (2.5)	
Holland	Hash	2 (0.8)	Home-grown Skunk/Sensimilla	4 (1.5)
	Imported herbal cannabis	1(0.4)	Nederwiet	174 (66.4)
	Geimporteerde Wiet	7 (2.7)	Nederhasj	29 (11.1)
			Geimporteerde Hasj	21 (8.0)
		Unknown	24 (9.2)	
Spain	Imported herbal cannabis	83 (33.9)	Hash	140 (57.1)
	Geimporteerde Wiet	1 (0.4)	Home-grown Skunk/Sensimilla	15 (6.1)
		Unknown	6 (2.4)	
France	Imported herbal cannabis	28 (26.9)	Hash	61 (58.7)
			Home-grown Skunk/Sensimilla	5 (4.8)
			Super Skunk	1 (1.0)
		Unknown	9 (8.7)	
Italy	Hash	53 (39.8)	Home-grown Skunk/Sensimilla	9 (6.8)
	Imported herbal cannabis	67 (50.4)	Super skunk	2 (1.5)
		Unknown	2 (1.5)	
TOTAL		**429 (42.4)**		**582 (57.6)**

Across all countries, the favorite substance used is hash, even though the varieties used have different potencies. In Holland 66.6% of the sample preferred Nederwiet, that is the local herbal variety. The 57.6% of the sample, considering cases and controls together, smoked cannabis with an absolute percentage of THC>10%. 2.6% of the sample declared that they were unaware of the type of cannabis they smoked (**Table 17**).

At this stage, I would acknowledge that there are not botanical reasons for dividing the cannabis populations either side of 10% THC, but it is probably the most pragmatic way of dividing the sample, according to the Potter et al. study (2008), which is relevant to the time of our data collection, all resin and imported herbal samples in UK showed a below 10% THC-absolute concentration, while over 80% of sinsemilla samples were above 10% THC.

Table 18 shows that both cases (77.8%) and controls (84.4%) mostly declared that they smoked cannabis because their friends were using it, but this was more common in controls than in cases (p=0.004). A small proportion of cases (9.8%) and controls (6.6%) declared they first tried cannabis because their family members were using it, but this was a little more present in cases (p=0.05). Cases were also more likely to report to have used cannabis in order to feel better, compared to controls (p<0.001).

Table 18. Motivations for First Cannabis Use of the Sample by Cases and Controls.

Variables	Cases	N	Controls	N	t-test o $\chi 2$	df	*p-value*
Friends were using it		**546**		**585**	**8.1**	**1**	**0.004**
Yes (N, %)	425 (77.8)		494 (84.4)				
No (N, %)	121 (22.2)		91(15.6)				
Family members were using it		**531**		**564**	**3.8**	**1**	**0.050**
Yes (N, %)	52 (9.8)		37 (6.6)				
No (N, %)	479 (90.2)		527 (93.4)				
To feel better		**530**		**564**	**48.4**	**1**	**<0.001**
Yes (N, %)	86 (16.2)		21 (3.7)				
No (N, %)	444 (83.8)		543 (96.3)				

Legend: degree of freedom.

Table 19 shows that both cases and controls, among those who were currently cannabis users (i.e. in the last 12 months) at the time of the interview (i.e. the onset for cases), smoke cannabis because they like its effect, without any difference between the two groups (p=0.500).

Table 19. Motivations for Current Cannabis Use of the Sample by Cases and Controls

Variables	Cases	N	Controls	N	t-test o $\chi 2$	df	*p-value*
Like effect		**185**		**136**	**0.45**	**1**	**0.500**
Yes (N, %)	109 (58.9)		75 (55.1)				
No (N, %)	76 (41.1)		61 (44.9)				
Feel relaxed		**185**		**137**	**4.1**	**1**	**0.044**
Yes (N, %)	150 (81.1)		98 (71.5)				
No (N, %)	35 (18.9)		39 (28.5)				
Feel less nervous		**182**		**137**	**16.1**	**1**	**<0.001**
Yes (N, %)	91 (50.0)		38 (27.7)				
No (N, %)	91 (50.0)		99 (72.3)				
Being more sociable		**182**		**136**	**5.4**	**1**	**0.019**
Yes (N, %)	62 (34.1)		30 (22.1)				
No (N, %)	120 (65.9)		106 (77.9)				
Do you think to stop cannabis one day?		**208**		**149**	**18.9**	**1**	**<0.001**
Yes (N, %)	149 (71.6)		73 (49.0)				
No (N, %)	59 (28.4)		76 (51.0)				

Legend: df=degree of freedom.

Cases are more likely than controls to smoke cannabis in order to feel relaxed (0.044), less nervous (<0.001) and more sociable (0.019). In spite of this, cases are also more likely to want to stop cannabis use one day (<0.001) (**Table 20**).

Additionally, cases also declared they had unpleasant effects from cannabis (i.e. to feel fearful, mad, nervy, suspicious, to hearing voices, to have visions) more often than controls (all p<0.001); however they declared also that they feel full of plans and ideas and better in understanding the world, more often than controls (all p<0.001), while controls are more likely to refer to feel happy after smoking cannabis, with respect to cases (p=0.004) (data not shown in tables).

2.6. Other Drug Use

Table 20 shows that cases are more likely to have smoked tobacco in the last 12 months ($p<0.001$) and in a larger amount than controls ($p=0.008$). Cases were also more likely to have used other illegal drugs ($p<0.001$), while controls were more likely to have used alcohol in the last 12 months ($p<0.001$).

Table 20. Pattern of Tobacco and Other Drug Use of the Sample by Cases and Controls.

Variables	Cases	N	Controls	N	t-test o $\chi 2$	df	*p-value*
Tabaco use - past 12 months		**809**		**1,008**	**212.7**	**1**	**<0.001**
Yes (N, %)	477 (59.0)		254 (25.2)				
Cigarette/day - past 12 moths	14.8 (16.9)	**469**	11.7 (10.7)	**257**	**2.6**	**724**	**0.008**
Other Drugs Use Lifetime		**834**		**1,061**	**58.2**	**1**	**<0.001**
Yes (N, %)	243 (22.9)		326 (39.1)				
Alcohol Yes (N, %)	431 (62.9)	**685**	649 (75.2)	**863**	**27.3**	**1**	**<0.001**

Legend: df=degree of freedom.

Table 21 describes frequencies and percentages of other drug consumption in the sample. The sum of percentages is more than 100% because some subjects have tried more than one drug in his/her lifetime. The table indicates the answer of the 568 (325 cases; 243 controls) people of the sample who used other drugs.

Table 21. Other Drugs: Type and Distribution.

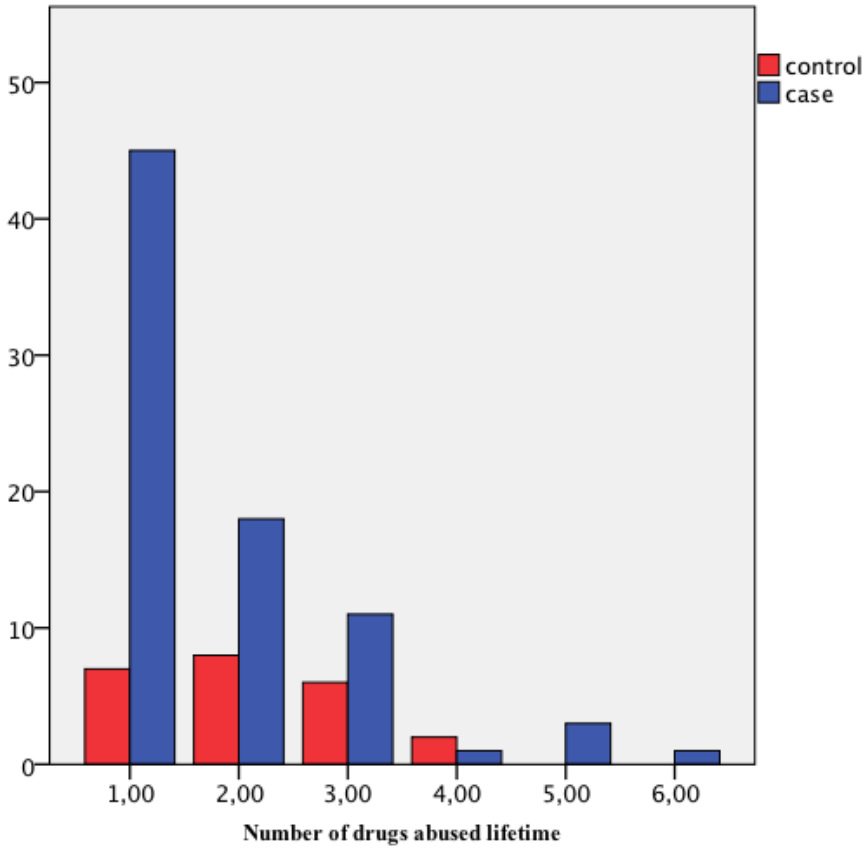
Drug Type	Total %	Cases N (%)	Controls N (%)	p-value	% Cases N=325*	%Controls N=243*	p-value
Cocaine	**20.2**	222 (26.7)	159 (15)	**<0.001**	68.3	65.4	0.471
Amphetamines/Stimulants	**18.2**	187 (22.4)	158 (14.9)	**<0.001**	57.5	65.0	0.060
Hallucinogens	**12.0**	114 (13.7)	114 (10.7)	0.052	34.8	46.9	**0.003**
Ketamine	**5.3**	64 (7.7)	37 (3.5)	**<0.001**	19.4	15.2	0.198
Inhalants	**4.6**	55 (6.6)	32 (3.0)	**<0.001**	16.6	13.2	0.257
Sedatives	**3.4**	40 (4.8)	25 (2.4)	**0.004**	12.0	10.3	0.523
Opioids	**3.3**	42 (5.0)	21 (2.0)	**<0.001**	5.0	2.0	**<0.001**
Crack	**3.0**	37 (4.4)	19 (1.8)	**0.001**	4.4	1.8	**0.001**
Other	**3.4**	34 (4.1)	30 (2.8)	0.135	10.2	12.3	0.410

*Among those who used other drugs

A part from Hallucinogens and Other substances, cases were more likely to have used any kind of other drug than controls. Among those who used other drugs, cases and controls did not differ very much in substance preferred, a part from opioids, and crack, wich were mostly preferred from psychotic patients, and hallucinogens, that were preferred by a higher percentage of controls, than cases.

103 subjects in total of those who used other illegal drugs declared to have abused of at least one of these drugs in their lifetime and this percentage was higher for cases (24.3%) than controls (9.5%) ($p<0.001$). Most of cases abused of one other illegal drug (see **Figure 14**).

Figure 14. Number Of Other Illegal Drugs Abused Lifetime.



Legend: This histogram represents number of subjects (Y axis) who abused of one or more drugs (X axis) in their lifetime.

2.7. Clinical Characteristics of Cases

Table 22 describes the distribution of the diagnoses in cases.

Table 22. Clinical Characteristics of Cases.

Diagnosis according to ICD-10	(N, %)	**Diagnosis according to DSM-IV-TR**	(N, %)
Non-affective Psychosis	**517 (74.5)**	**Non affective Psychosis**	**552 (75.5)**
Schizophrenia (F20)	275 (39.6)	Schizophrenia	216 (29.5)
Schizoaffective Disorder (F25)	29 (4.2)	Schizophreniform Disorder	152 (20.8)
Delusional Disorder (F22)	37 (5.3)	Schizoaffective Disorder	37 (5.0)
Other Non-Organic Psychosis (F29)	176 (25.4)	Delusional Disorder	26 (3.6)
		Psychosis NOS	121(16.6)
Affective Psychosis	**177 (25.5)**	**Affective Psychosis**	**179 (24.5)**
Major depressive disorder with psychotic features (F323, F333)	79 (11.4)	Major Depressive Disorder with psychosis	89 (12.2)
Bipolar disorder with psychotic features (F312, F315)	98 (14.1)	Bipolar I with psychosis	90 (12.3)
TOT	**694**		**731**

517 (74.5%) subjects met criteria for a diagnosis of F20-29 non-affective psychosis, 275 (39.6%) of them encountered ICD-10 criteria for the diagnosis of F20 schizophrenia.

The remaining 25.5% of the sample (177 subjects) met ICD-10 criteria for F30-33 affective psychoses. The proportions were similar using DSM-IV-TR criteria, with a 75.5% of the sample meeting criteria for non-affective psychosis and 24.5% of its meeting criteria for affective psychosis. As already mentioned, in the EU-GEI study we used ICD-10 criteria.

3. Principal Component Analysis (PCA) of PAS

PAS scores were manipulated. First of all, a reverse score was calculated in order to have higher scores for better adjustment, thus having scores comparable to IQ

derived from WAIS. In order to reduce the dimensionality of PAS, a principal-component analysis (PCA) on its nine scales was run.

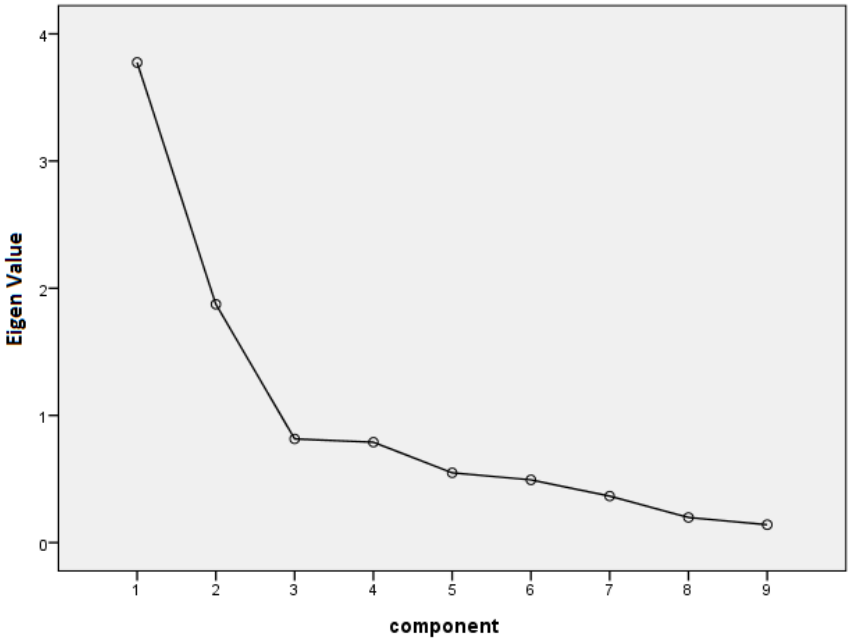
- Sociability: Childhood (Soc<12), Early Adolescence (Soc 16);
- Peer Relationships: Childhood (Peer<12), Early Adolescence (Peer 16);
- Scholastic Performance: Childhood (Schol<12), Early Adolescence (Schol 16);
- Adaptation to School: Childhood (Adap<12), Early Adolescence (Adap 16);
- Socio-Sexual Aspects During Early Adolescence (Sex 16).

The Kaiser-Mayer-Olkin measure verified the sampling adequacy for the analysis (KMO=0.670) and the Bartlett's test of sphericity ($\chi 2(36) = 8153,42$; $p<0.0001$) indicated that correlations between scales were sufficiently large for PCA. Firstly, an oblique rotation (theoretically oriented) was applied, that demonstrated a negligible correlation between the extracted factors (*rho*=0.306). Then the orthogonally rotated solution (Pedhazur & Schmelkin, 1991) was preferred, in order to convert this set of possibly correlated variables into a set of linearly uncorrelated variables (*rho*=0) (**Table 23**; **Figure 15**).

Table 23. Principal-Component Analysis.

Components	Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of variance	% cumulative	Total	% of variance	% cumulative
1 - Soc<12	**3.775**	**41.945**	**41.945**	**3.140**	**34.894**	**34.894**
2 – Soc 16	**1.874**	**20.823**	**62.768**	**2.509**	**27.874**	**62.768**
3 - Peer<12	.815	9.058	71.826	-	-	-
4 – Peer 16	.789	8.771	80.598	-	-	-
5 - Schol<12	.549	6.097	86.694	-	-	-
6 – Schol 16	.493	5.482	92.176	-	-	-
7 - Adap<12	.366	4.062	96.238	-	-	-
8 – Adap 16	.198	2.198	98.436	-	-	-
9 – Sex 16	.141	1.564	100.000	-	-	-

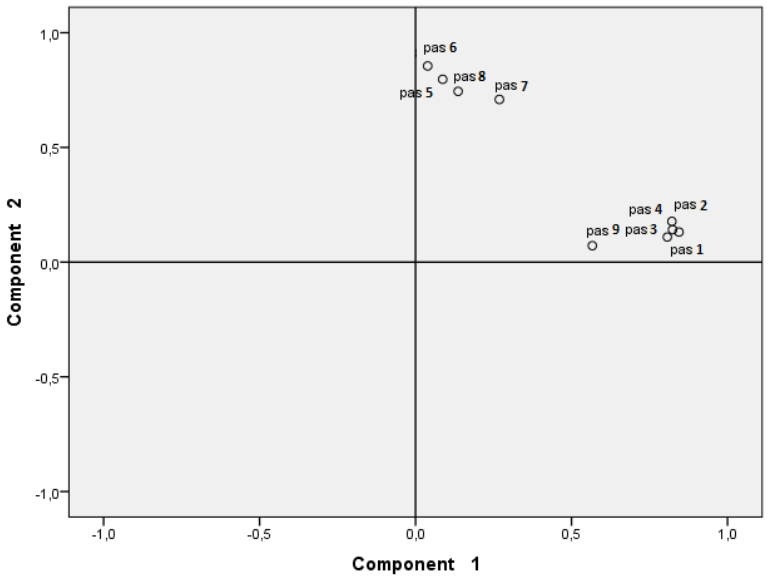
Figure 15. Graph of the Eigen Values (Scree plot).



Legend: Kraiser's criterion (dashed line).

According to Kraiser's criterion (see **Figure 16**), only eigen values >1 were considered, so two factors were retained in the final analysis.

Figure 16. Factor loading after rotation



The rotated components matrix (**Table 24**) shows five scales (Sociability in Childhood and in Early Adolescence, Relationships with Peer in Childhood and in Early Adolescence and Socio-Sexual Aspects of Life During Early Adolescence) that cluster on **Factor 1**, that represents the Premorbid Social Factor (**PSF**), while the other four scales (Scholastic Performance in Childhood and in Early Adolescence and Adaptation to School in Childhood and in Early Adolescence) cluster on **Factor 2**, thus representing the Premorbid Academic Factor (**PAF**).

Table 24. Factor loading after rotation.

Components	1	2
1 - Soc<12	.807	.109
2 – Soc 16	.845	.131
3 - Peer<12	.824	.142
4 – Peer 16	.822	.177
5 - Schol<12	.087	.797
6 – Schol 16	.039	.855
7 - Adap<12	.269	.709
8 – Adap 16	.136	.744
9 – Sex 16	.567	.072

From this analysis we can also derive the information that PSA factor is able to explain 34.9% of the variance while PAF factor the 27.9%. This result indicates that social adjustment factor is able to explain the greater part of the premorbid adjustment in childhood and early adolescence. Finally, the Cronbach-α for PAS is 0.816, thus indicating a high reliability and it is <0.815 for all the dimensions and this suggests that it is not necessary to remove some scales of the PAS in order to increase the reliability of the test.

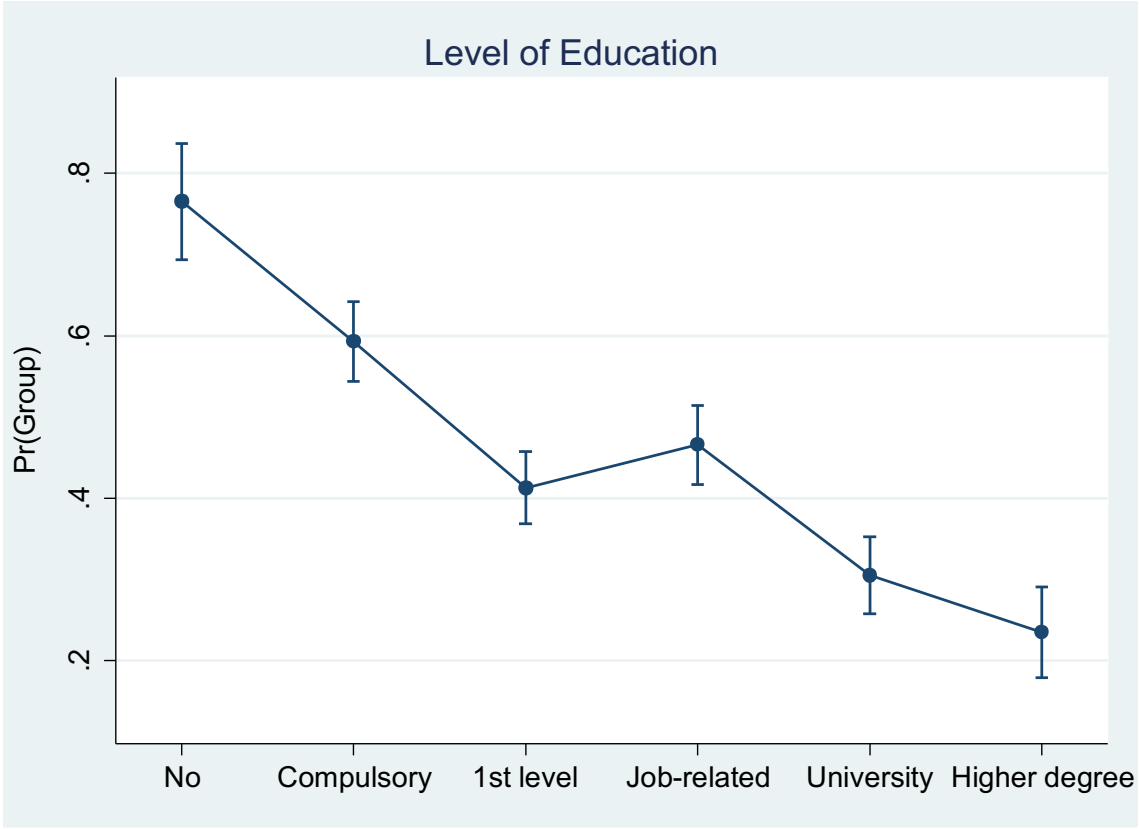
4. Aggregated sociodemographic-categories

Some variables of interest were analyzed using logistic regressions in order to predict which of groups (case or control) a person is likely to belong to given certain information.

4.1. Level of Education

People with higher university degree have the same probability to belong to the case group compared to people who achieved a first university degree (p=0.971), thus it is possible to aggregate these two categories. Moreover, it is possible to aggregate the job-related education and the first level education categories (p=1.00) (**Figure 17**).

Figure 17. Level of Education: Categories Aggregation.



Legend: the graph reports a logistic regression on the "Level of education" variable: on the X axis are represented the categories of the variable, on the Y axis is expressed the probability of a person to belong to the case group, in terms of percentages.

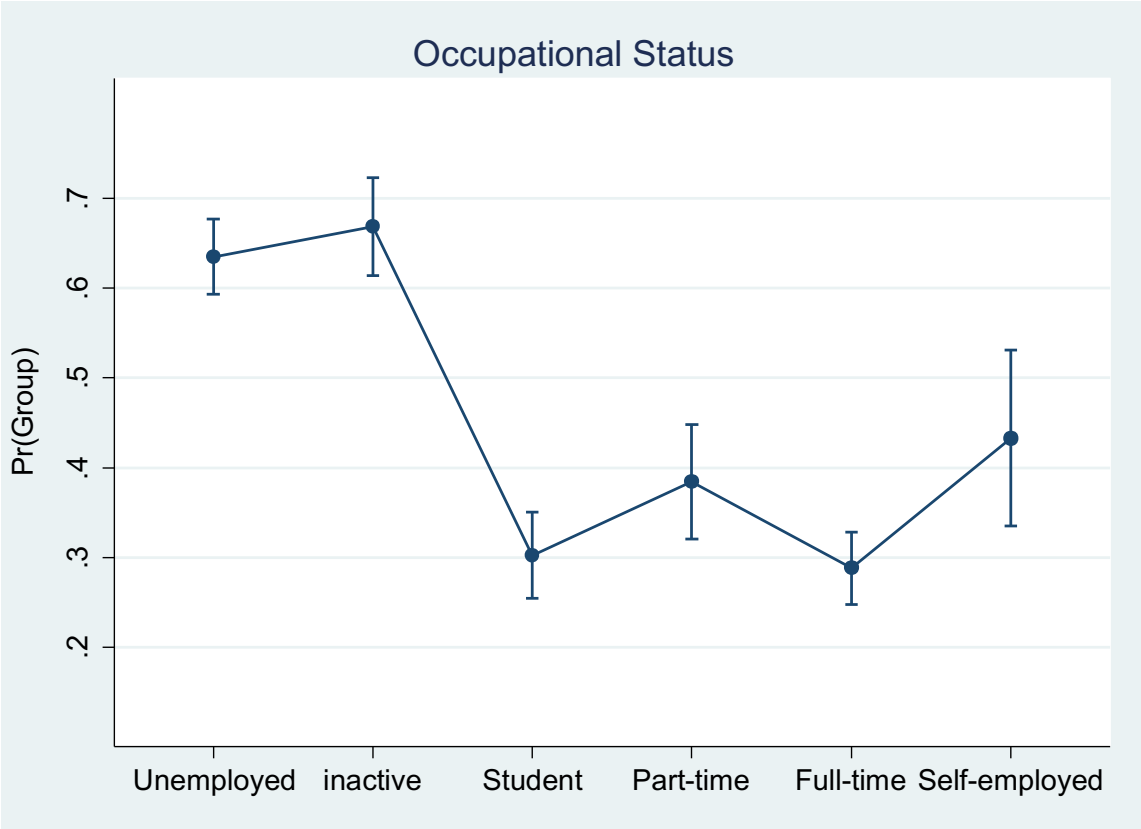
Thus, the new variable will be constituted of four main categories:

- Code 0. University education;
- Code 1. First Level education;
- Code 2. Compulsory Education;
- Code 3. No education.

4.2. Occupational Status

People unemployed have the same probability to belong to the case group compared to people who are economically inactive (p=1.00), thus it is possible to aggregate these two categories. Moreover, it is possible to aggregate student, part-time, full-time employed and self-employed categories (p-range=0.076-1.00) (**Figure 18**).

Figure 18. Occupational Status: Categories Aggregation.



Legend: the graph reports a logistic regression on the "Occupational Status" variable: on the X axis are represented the categories of the variable, on the Y axis is expressed the probability of a person to belong to the case group, in terms of percentages.

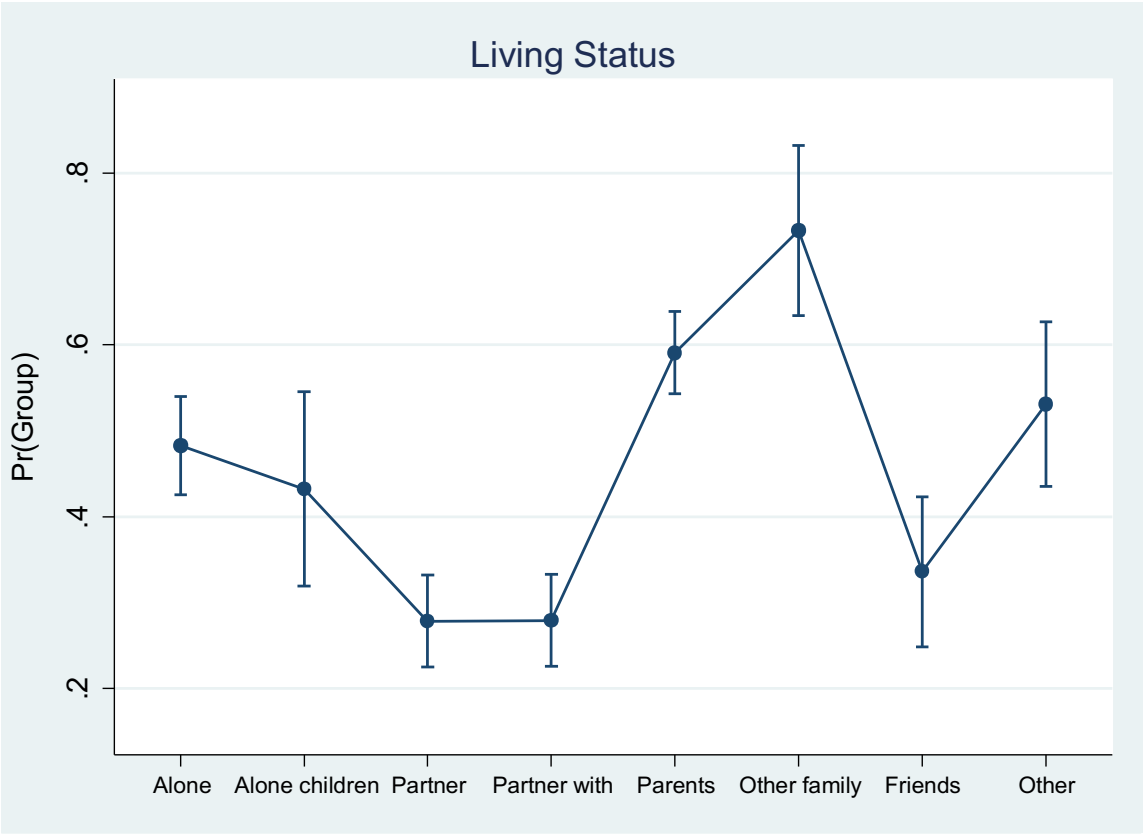
The new variable will be constituted of two only categories:

- Code 0. Employed-Student;
- Code 1. Unemployed-Economically Inactive.

4.4. Living Status

People living with their parents have the same probability to belong to the case group compared to people who live with other families or with others (not friends) (p-range=0.161-1.00), thus it is possible to aggregate these three categories. It is also possible to aggregate the remaining categories (p-range=0.325-1.00) (**Figure 19**). Living alone was not aggregated to other categories, given that it was reported as a risk factor for psychosis (C Morgan et al., 2008; Stilo et al., 2013).

Figure 19. Living Status: Categories Aggregation.



Legend: the graph reports a logistic regression on the "Living Status" variable: on the X axis are represented the categories of the variable, on the Y axis is expressed the probability of a person to belong to the case group, in terms of percentages.

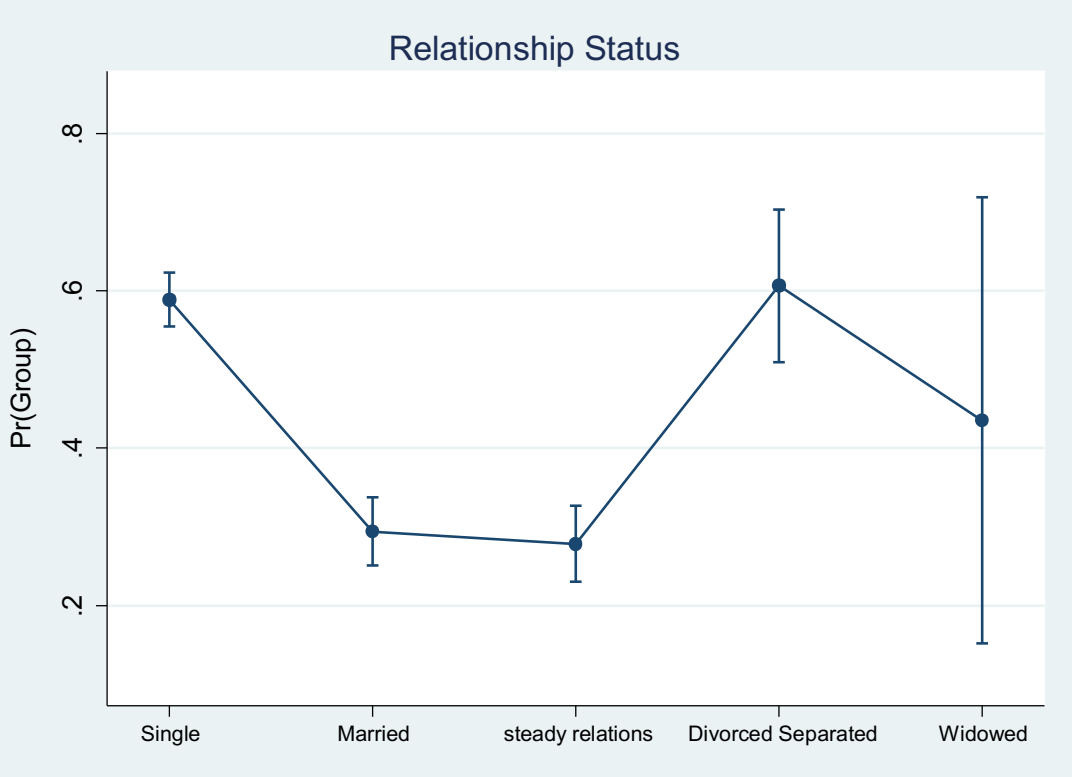
The new variable will be constituted of the following three categories:

- Code 0. Partner, partner with children, friends, alone with children;
- Code 1. Alone;
- Code 2. Parents, other family and other.

4.5. Relationship Status

People married have the same probability to belong to the case group compared to people in a steady relationship (p=1.00), thus it is possible to aggregate these two categories. It is also possible to aggregate people divorced with people widowed (p=1.00) (**Figure 20**). Being single is not aggregated to other categories (i.e. being separated or widowed) for theorical reasons, given that it was reported as a risk factor for psychosis (C Morgan et al., 2008; Stilo et al., 2013).

Figure 20. Relationship Status: Categories Aggregation.



Legend: the graph reports a logistic regression on the "Relationship Status" variable: on the X axis are represented the categories of the variable, on the Y axis is expressed the probability of a person to belong to the case group, in terms of percentages.

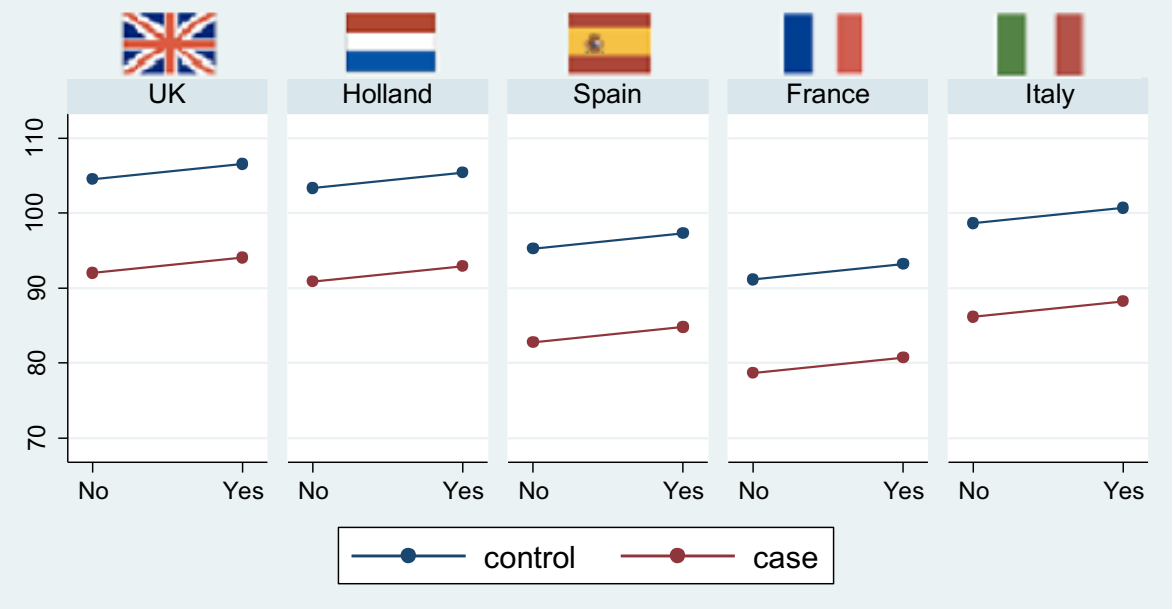
The new variable will be categorized as follow:

- Code 0: Married/in a steady relationship;
- Code 1: Divorced/Separated/Widowed;
- Code 2: Single.

5. IQ and Cannabis Use by Country

I first tried to replicate the analysis performed in my previous study, by performing an ANCOVA with IQ as dependent variable and cannabis (Yes/No) and subject status (Cases/Controls) as independent variables, along with Country. The model was adjusted by age, gender, ethnicity, occupation and education. Cases are lower in IQ than controls after controlling for possible confounders ($p<0.001$). Both patients and controls who smoked cannabis in their lifetime have a 2.02 points higher IQ than their respective no-cannabis groups ($p=0.015$) (**Table 25**). The relationship is similar across different countries but shifts ($p<0.05$). (**Figure 21**).

Figure 21. IQ Scores in Cases and Controls by Cannabis Use Across Countries.



Legend: This graph describes IQ scores (Y axis) in cases and controls cannabis users and not users across different countries (X axis). Adjusted for Country, age, gender, ethnicity, occupation and education. Bonferroni.

Table 25. Main Effects of Cannabis Use and Group Belonging on IQ across Different Countries.

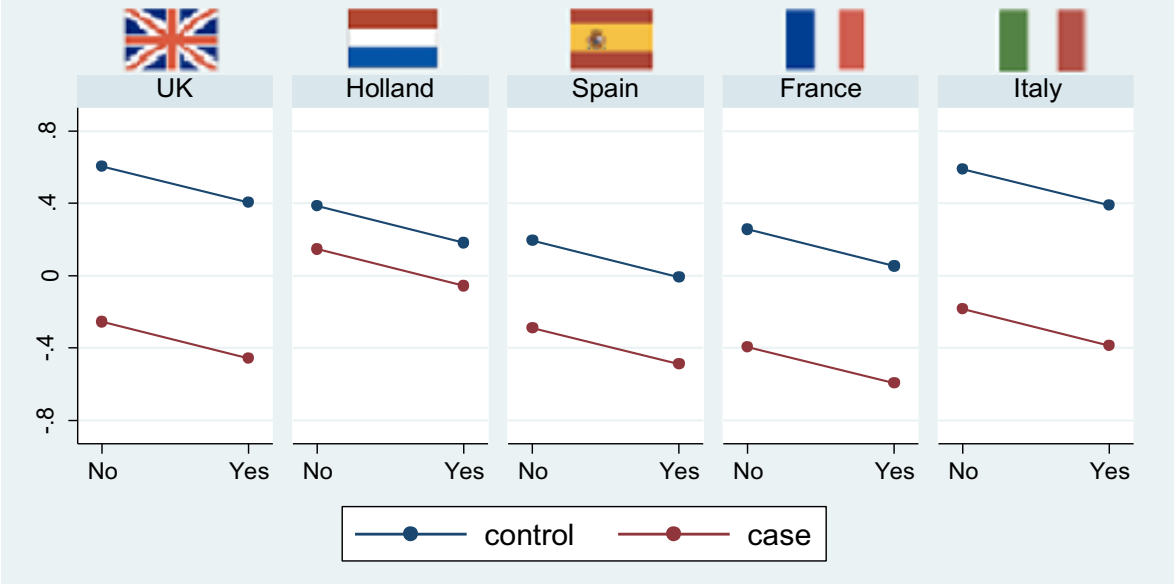
Variables	Coefficient	S.E.	t-test	p-value	95% C.I.	
Cannabis Yes vs. No	2.014	0.825	2.44	**0.015**	0.395	3.633
Group Cases vs. Controls	-12.423	0.884	-14.05	**<0.001**	-14.157	-10.688

Legend: SE= Standard Error; C.I.= Confidence Interval.

6. Premorbid Academic Factor and Cannabis Use by Country

Premorbid Academic Factor (PAF) before 16 years derived from PSA scales, was entered as dependent variable in an ANCOVA model with cannabis (Yes/No) and subject status (Cases/Controls) as independent variables. Country was included in the model as a fixed factor and the model was adjusted by age, gender and ethnicity. Education and occupation were not taken into account because they are strictly related to and a consequence of premorbid academic adjustment. As is shown in **Figure 22**, cases have a worse PAF scores than controls after controlling for possible confounders ($p<0.001$). PAF results were worst in both patients and controls who smoked cannabis in their lifetime than patients who did not ($p<0.001$) (**Table 26**), and this relationship in relation to cannabis is the same across all countries, but shifts, because differences in cases and controls ($p<0.05$).

Figure 22. PAF Scores in Cases and Controls by Cannabis Use Across Countries.



Legend: This graph describes PAF scores (Y axis) in cases and controls cannabis users and not users across different countries (X axis). Adjusted for Country, age, gender and ethnicity. Bonferroni.

Table 26. Main Effects of Cannabis Use and Group Belonging on PAF across Different Countries.

Variables	Coefficient	S.E.	t-test	p-value	95% C.I.	
Cannabis Yes vs. No	-0.200	0.046	-4.30	**<0.001**	-0.292	-0.109
Group Cases vs. Controls	-0.600	0.047	-12.55	**<0.001**	-0.694	-0.506

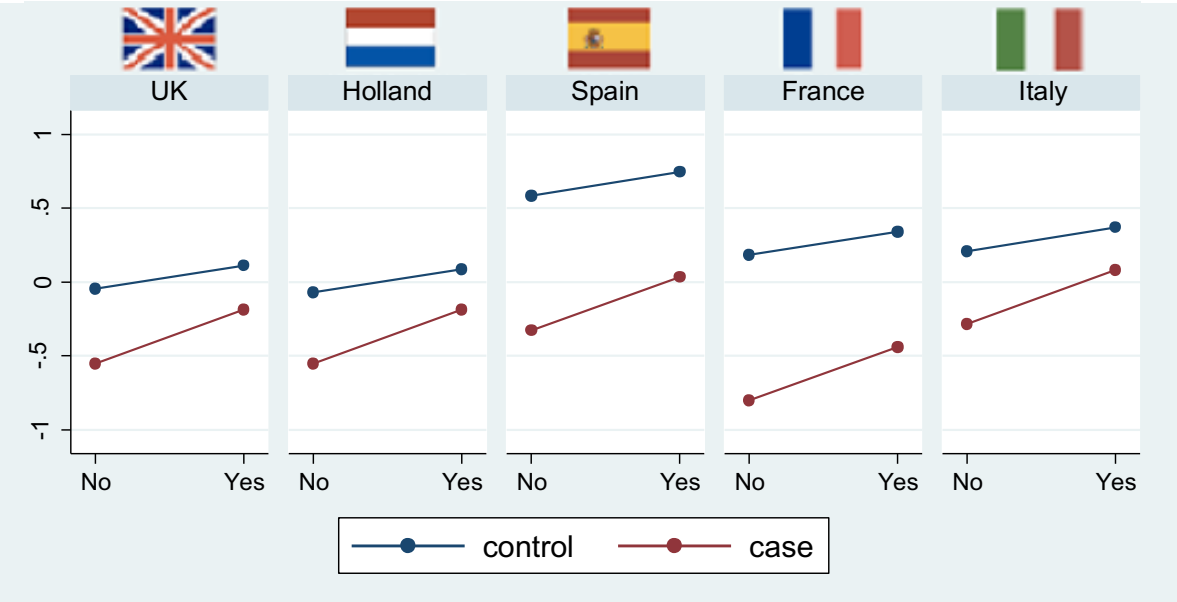
Legend: SE= Standard Error; C.I.= Confidence Interval.

7. Premorbid Social Factor and Cannabis Use by Country

Premorbid Social Factor (PSF) before 16 years derived from PSA scales, was entered as dependent variable in an ANCOVA model with cannabis (Yes/No) and subject status (Cases/Controls) as independent variables. Country was included in the model as a fixed factor and the model was adjusted by age, gender and ethnicity.

Cases have a worse PSF than controls once corrected for confounders ($p<0.001$) (**Figure 23**). Conversely to PAF, PSF results better in patients who smoked cannabis in their lifetime than patients who did not ($p=0.009$), but there are tiny differences in controls in PSF scores ($p=0.053$), according to cannabis use (interaction $p=0.030$) (**Table 27**). These results are similar across all countries, but shift because of differences in cases and controls social behaviour ($p<0.05$).

Figure 23. PSF Scores in Cases and Controls by Cannabis Use Across Countries.



Legend: This graph describes PSF scores (Y axis) in cases and controls cannabis users and not users across different countries (X axis). Adjusted for Country, age, gender and ethnicity. Bonferroni.

Table 27. Effects of Cannabis Use and Group Belonging on PSF across Different Countries.

Variables	Coefficient	S.E.	t-test	p-value	95% C.I.	
Cannabis Yes vs. No	0.159	0.060	-2.62	**0.009**	0.039	0.278
Group Cases vs. Controls	-0.505	0.106	-4.73	**<0.001**	-0.715	-0.295
Cannabis Yes x Group	0.204	0.094	2.17	**0.030**	0.019	0.390

Legend: SE= Standard Error; C.I.= Confidence Interval.

8. Conclusions About Cannabis Use on IQ, PAF and PSF

These analyses show that, across all European Countries studied, both cases (68.4%) and controls (55.7%) that reported a lifetime cannabis use have a higher IQ than cases and controls who did not.

Conversely, both cases and controls that smoked cannabis in their lifetime, reported a worse academic adjustment before 16 years and cases, but not controls, also reported a better premorbid social adjustment before their 16 years.

9. Data Manipulation for a Comprehensive Model

Given these preliminary results, with contradictive findings on IQ and academic premorbid adjustment, I wanted to perform a Multivariate Analysis of Variance (MANOVA) with IQ, PAF and PSF standardized score as outcomes and group (Cases/Controls) and cannabis use (Never/Less Than Everyday/Everyday) as fixed factors.

Country, age, gender and ethnicity were also included as possible confounders. In order to construct the model, correlations between these three outcomes and their standardization were performed. Different pattern of cannabis use was observed to establish which categories could be aggregated.

8.1. Correlation of IQ, PAF and PSF scores and Standardization of IQ

First of all, bivariate correlations between IQ and PAF and PSF scores were controlled and, as is shown in **Table 28**, IQ was related to PAF (*rho*= 0.46, p<0.001) but not to PSF (*rho*= 0.03, p=0.163), apparently in a counterintuitive relationship with my previous results.

Then, IQ scores were standardized in *z-scores*, in order to obtain mean 0 and standard deviation 1.

Table 28. Bivariate Pearson's Correlations Between IQ, PAF and PSF.

		IQ	PSF	PAF
IQ	Pearson Correlation	1	0.034	0.460**
	Sig. (2-tailed)		0.163	**0.000**
	N	1739	1718	1718
PSF	Pearson Correlation	0.034	1	0.000
	Sig. (2-tailed)	0.163		1,000
	N	1718	1867	1867
PAF	Pearson Correlation	0.460**	0.000	1
	Sig. (2-tailed)	**0.000**	1,000	
	N	1718	1867	1867

Legend ** Correlation is significant at the 0.01 level (2-tailed).

8.2. Aggregated Categories of Different Patterns of Cannabis Use

I performed a logistic regression on the variable "frequency of cannabis use" in order to predict which groups (case or control) a person is likely to belong to given certain pattern of cannabis use. Frequency is an indicator of the amount of cannabis intake in the period of life in which cannabis was mostly used.

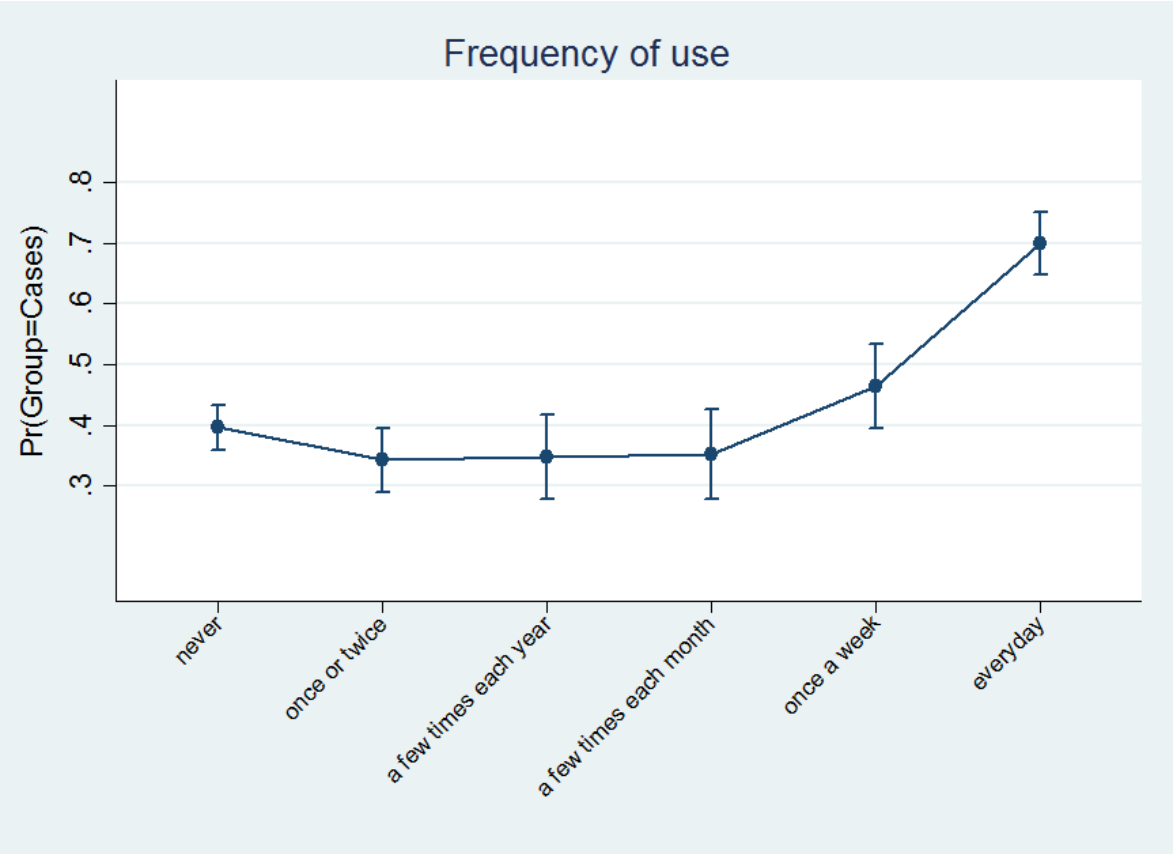
As is shown in **Figure 24**, people who smoked cannabis everyday at any time in their lifetime, are 3.9 folds more likely to be cases than "never used" group (OR=3.9, C.I. 95%=2.87-5.35, p<0.001), i.e. the probability to be cases is equal to 70% for people who smoked cannabis everyday, while people who never used cannabis have only the 39.6% of probability to be cases.

Everyday use of cannabis was the only category able to be separated from the others from a statistical point of view, while we separated "never-users" for theoretical reasons. This analysis was adjusted for age, gender and ethnicity.

The new variable will be categorized as follow:

- Code 0: Never;
- Code 1: Less than everyday;
- Code 2: Everyday.

Figure 24. Frequency of Cannabis Use: Categories Aggregation.



Legend: the graph reports a logistic regression on the "Frequency of cannabis Use" variable: on the X axis are represented the categories of the variable, on the Y axis is expressed the probability of a person to belong to the case group, in terms of percentages. Adjusted for age, gender and ethnicity.

10. Characteristics of the sample by Frequency of cannabis Use

I first explored the descriptive characteristics of the sample by frequency of cannabis use.

Table 29 describes the frequency of cannabis use by Country and stratified by case/control status, that shows evident differences in the distribution of frequent users.

Holland has the highest proportion of everyday users, in the case group, followed by Spain ($p<0.001$). Interestingly, there are no differences in control group by frequency of cannabis use ($p=0.081$).

Table 29. Frequency of cannabis use across different Countries.

Variables		Never	N	Less than Everyday	N	Everyday	N	χ2	df	*p-value*
CASES	**Country**, N (%)		**263**		**307**		**256**	**41.1**	**8**	**<0.001**
	UK	60 (28.6)		94 (44.8)		56 (26.7)				
	Holland	40 (20.8)		73 (38.0)		79 (41.1)				!!
	Spain	63 (31.3)		70 (34.8)		68 (33.8)				!
	France	46 (45.1)		26 (25.5)		30 (29.4)				
	Italy	54 (44.6)		44 (36.4)		23 (19.0)				
CONTROLS	**Country**, N (%)		**470**		**508**		**81**	**14.0**	**8**	0.081
	UK	146 (42.3)		169 (49.0)		30 (8.7)				
	Holland	94 (42.7)		108 (49.1)		18 (8.2)				
	Spain	96 (44.2)		105 (48.4)		16 (7.4)				
	France	83 (57.6)		53 (36.8)		8 (5.6)				
	Italy	51 (38.3)		73 (54.9)		9 (6.8)				

Legend: df= degree of freedom

Overall, cannabis users in our sample are generally males and younger than not-users (data not shown in tables), and **Table 30** shows that everyday users have an even higher proportion of males and are younger than less than everyday users, both in cases and in controls ($p<0.001$). While in controls less than everyday users are mostly white people ($p<0.001$), this difference is attenuated in cases (0.057).

Table 31 shows that both cases and controls with a University degree were more likely to have used cannabis at least once in their life, but less than everyday ($p<0.001$). Additionally, those with less than everyday cannabis use, have more years of education in both cases ($p=0.001$) and controls ($p<0.001$). Less than everyday users are also more likely to be employed or students in both cases ($p<0.001$) and controls ($p=0.014$), while everyday users are more likely to be unemployed in cases, but not in controls.

Finally, everyday and less than everyday users are mostly single in cases ($p<0.001$), while in controls they mostly have a partner ($p=0.003$). Everyday users are also more likely to live with their parents or in other families or institutions than less than everyday and never users in case group ($p<0.001$), but not in controls ($p=0.103$) (**Table 32**).

Table 30. **Socio-demographic Characteristics of the Sample by Frequency of Cannabis Use.**

Variables	Never	N	Less than Everyday	N	Everyday	N	χ2 or t-test	df	*p-value*
CASES									
Gender, N (%)		**263**		**307**		**256**	**74.5**	**2**	**<0.001**
Male	113 (21.8)		204 (39.3)		202 (38.9)				
Female	150 (48.9)		103 (33.6)		54 (17.6)				
Age,		**263**		**306**		**256**	**45.5**	**2**	**<0.001**
Mean (SD)	34.8 (12.1)		29.1 (9.3)		26.8 (7.7)				
Ethnicity, N (%)		**262**		**305**		**256**	**9.1**	**4**	0.057
White	164 (30.8)		213 (40.0)		156 (29.2)				
Black	51 (37.2)		46 (33.6)		40 (29.2)				
Other	47 (30.7)		46 (30.1)		60 (39.2)				
CONTROLS									
Gender, N (%)		**470**		**508**		**81**	**23.0**	**2**	**<0.001**
Male	191 (38.0)		258 (51.3)		54 (10.7)				
Female	279 (50.2)		250 (45.0)		27 (4.9)				
Age,		**470**		**507**		**80**	**18.6**	**2**	**<0.001**
Mean (SD)	39.4 (14.1)		34.5 (12.5)		34.6 (11.3)				
Ethnicity, N (%)		**466**		**502**		**80**	**17.7**	**4**	**0.001**
White	347 (41.6)		426 (51.0)		62 (7.4)				
Black	58 (55.8)		35 (33.7)		11 (10.6)				
Other	61 (56.0)		41 (37.6)		7 (6.4)				

Legend: SD=standard deviation; df=degree of freedom.

Table 31. **Characteristics of the Sample by Frequency of Cannabis Use: Education and Work.**

Variables	Never	N	Less than Everyday	N	Everyday	N	χ2 or t	df	*p-value*
CASES									
Education, N (%)		**262**		**306**		**256**	**22.6**	**6**	**0.001**
No qualification	37 (33.3)		28 (25.2)		46 (41.4)				
Compulsory Edu.	65 (30.2)		79 (36.7)		71 (33.0)				
1st Degree Edu.	107 (30.4)		131 (37.2)		114 (32.4)				
University	53 (36.3)		68 (46.6)		25 (17.1)				
Years of Edu.,		**260**		**307**		**255**	**4.5**	**2**	**0.001**
Mean (SD)	13.1 (4.1)		14.1 (4.1)		13.3 (3.6)				
Occupation, N (%)		**256**		**303**		**252**	**21.7**	**2**	**<0.001**
Uneployed	138 (29.7)		152 (32.8)		174 (37.5)				
Employed/Student	118 (34.0)		151 (43.5)		78 (22.5)				

CONTROLS								
Education, N (%)	**470**		**508**		**81**	**21.1**	**6**	**0.002**
No qualification	12 (40.0)		12 (40.0)		6 (20.0)			
Compulsory Edu.	76 (53.5)		52 (36.6)		14 (9.9)			
1st Degree Edu.	193 (42.8)		218 (48.3)		40 (8.9)			
University	189 (43.3)		226 (51.8)		21 (4.8)			
Years of Edu.,	**470**		**508**		**81**	**9.8**	**2**	**<0.001**
Mean (SD)	15.0 (3.8)		15.9 (3.8)		14.2 (3.4)			
Occupation, N (%)	**453**		**483**		**74**	**8.5**	**2**	**0.014**
Uneployed	128 (49.2)		106 (40.8)		26 (10.0)			
Employed/Student	325 (43.3)		377 (50.3)		48 (6.4)			

Legend: df= degree of freedom. Abbreviations: Edu. = Education.

Table 32. Characteristics by Frequency of Cannabis Use: Relationship and Living Status.

Variables	Never	N	Less than Everyday	N	Everyday	N	χ2	df	*p-value*
CASES									
Relationship, N (%)		**243**		**277**		**233**	**26.6**	**4**	**<0.001**
Single	89 (25.6)		123 (35.3)		136 (39.1)				
Partner	103 (39.0)		92 (34.8)		69 (26.2)				
Separated	51 (36.1)		62 (44.0)		28 (19.9)				
Living with, N (%)		**257**		**303**		**250**	**24.4**	**4**	**<0.001**
Part./ Friends/ Child	85 (39.9)		90 (42.3)		38 (17.8)				
Alone	39 (28.3)		53 (38.4)		46 (33.3)				
Parents/Other	133 (29.0)		160 (34.9)		166 (36.2)				
CONTROLS									
Relationship, N (%)		**421**		**448**		**66**	**16.1**	**4**	**0.003**
Single	57 (36.3)		79 (50.3)		21 (13.4)				
Partner	238 (48.6)		223 (45.5)		29 (5.9)				
Separated	126 (43.8)		146 (50.7)		16 (5.6)				
Living with, N (%)		**453**		**481**		**74**	**7.7**	**4**	0.103
Part./ Friends/ Child	286 (47.7)		276 (46.0)		38 (6.3)				
Alone	59 (37.1)		83 (52.2)		17 (10.7)				
Parents/Other	108 (43.4)		122 (49.0)		19 (7.6)				

Legend: df= degree of freedom. Abbreviations: Part.= partner.

In terms of pattern of cannabis use, **Table 33** describes differences between less than everyday users and everyday users.

Table 33. Patterns of Cannabis Use by Frequency in Cases and Controls.

Variables	Less than Everyday	N	Everyday	N	χ2 or t-test	df	*p-value*
CASES							
Current Use, N (%)		**305**		**256**	**13.4**	**1**	**<0.001**
Yes	88 (44.0)		112 (56.0)				
No	217 (60.1)		144 (39.9)				
Age at First Use,		**306**		**255**	**12.5**	**1**	**<0.001**
Mean (SD)	17.5 (5.1)		16.1 (2.9)				
Tolerance Increased Amount, N (%)		**289**		**242**		**1**	**<0.001**
Yes	33 (19.4)		137 (80.6)				
No	256 (70.9)		105 (29.1)				
Mode of use, N (%)		**278**		**250**	**71.5**	**1**	**<0.001**
Socially	237 (64.9)		128 (35.1)				
On my Own	41 (25.2)		122 (74.8)				
Type, N (%)		**250**		**250**	**15.6**	**1**	**<0.001**
Low-THC <10%	107 (62.2)		65 (37.8)				
High-THC <10%	143 (43.6)		185 (56.4)				
CONTROLS							
Current Use, N (%)		**506**		**81**	**8.7**	**1**	**0.005**
Yes	111 (78.7)		30 (21.3)				
No	395 (88.6)		51 (11.4)				
Age at First Use,		**508**		**81**	**22.1**	**1**	**<0.001**
Mean (SD)	18.2 (4.6)		15.6 (2.9)				
Tolerance Increased Amount, N (%)		**497**		**75**		**1**	**<0.001**
Yes	27 (43.5)		35 (56.5)				
No	470 (92.2)		40 (7.8)				
Mode of use, N (%)		**491**		**80**	**87.9**	**1**	**<0.001**
Socially	468 (90.3)		50 (9.7)				
On my Own	23 (43.4)		30 (56.6)				
Type, N (%)		**433**		**78**	**1.6**	**1**	0.122
Low-THC <10%	223 (86.8)		34 (13.2)				
High-THC <10%	210 (82.7)		44 (17.3)				

Legend: df= degree of freedom; SD= standard deviation.

Everyday users are more likely to be current users both in cases (p<0.001) and in controls (p=0.005), and to have started at a younger age in both groups (p<0.001). Cases and controls everyday smokers were also more likely to declare that tolerance has increased the amount of cannabis they used (p<0.001), and they were also more

likely to smoke cannabis alone, while the opposite was true for less than everyday smokers, that were more socially smokers ($p<0.001$). Finally, among cases ($p<0.001$) but not among controls ($p=0.122$), everyday smokers were also more likely to have preferentially chosen high potency cannabis. Everyday users were more likely to have used other drugs than less than everyday users in cases ($p<0.001$) but the opposite was true in control group, where less than everyday users have used more other illegal drugs than everyday cannabis users ($p<0.001$) (data not shown in tables). Given these differences, I wanted to proceed with the analysis on the three different outcomes by frequency of cannabis use.

11. Multivariate Analysis of the Variance on IQ, PAF and PSF

Results from MANOVA were derived from 1,739 observations (cases and controls with complete information on PAS, CEQ and WAIS). Using Roy's largest root test, there was a significant effect of both group ($R = 0.195$, F (3, 1689) $=109.64$, $p<0.001$) and frequency of cannabis use ($R = 0.043$, F (3, 1690) $= 24.05$, $p<0.001$) in determining IQ, PSF and PAF scores. There was also a significant interaction effect ($R = 0.0058$, F (3, 1690) $= 3.27$, $p = 0.020$) between group and frequency of cannabis use. Thus it was possible to look at the separate ANOVAs on the outcome variables, corrected by Bonferroni, by including Country, age, gender and ethnicity as additional fixed factors. Education and occupation were not taken into account because they are related to and/or predicted from PAF.

11.1. IQ and Frequency of Cannabis Use

Regarding IQ, cases are lower in IQ than controls (F (1,1693) $= 297.5$, $p<0.001$) and there is also an effect of frequency of cannabis use overall (F (2,1693) $= 3.98$, $p=0.018$), but not interaction effect between cannabis and group ($p=0.647$). Looking at multiple comparisons, adjusted by Bonferroni, both cases and controls who smoked cannabis less than everyday have a higher IQ ($p=0.026$) compared with

never users, while there are no differences between everyday users and never users (p=1.000) nor between everyday and less than everyday users (0.224) (**Table 34**).

Table 34. ANOVA on IQ scores, corrected by Bonferroni.

Variables	Contrast	SE	t-test	*p-value*	95% C.I.	
Group						
Cases *vs* Controls	-0.770	0.044	-17.25	**<0.001**	-0.858	-0.683
Frequency of use						
Less everyday *vs* Never	0.120	0.045	2.63	**0.026**	0.010	0.229
Everyday vs Never	0.013	0.062	0.22	1.000	-0.136	0.164
Everyday vs Less everyday	-0.106	0.059	-1.78	0.224	-0.249	0.036

Legend: SE= Standard Error; C.I.= Confidence Interval.

11.2. Premorbid Academic Factor and Frequency of Cannabis Use

Regarding Premorbid Academic Factor (PAF), cases score worse in their premorbid academic adjustment compared to controls (F (1,1693) = 107.2, p<0.001) and there is also a significant effect of cannabis use (F (2,1693) = 23.8, p<0.001) but not an interaction effect between cannabis and group (p=0.1843).

Looking at multiple comparisons, adjusted by Bonferroni, both cases and controls everyday smokers score worse in premorbid academic adjustment than never users (p<0.001) and less than everyday users (p<0.001). There are no differences between less than everyday users and never users in premorbid academic adjustment (**Table 35**).

Table 35. ANOVA on PAF scores, corrected by Bonferroni.

Variables	Contrast	SE	t-test	*p-value*	95% C.I.	
Group						
Cases *vs* Controls	-0.507	0.048	-10.36	**<0.001**	-0.603	-0.411
Frequency of use						
Less everyday *vs* Never	-0.107	0.050	-2.15	0.094	-0.228	0.012
Everyday vs Never	-0.471	0.068	-6.84	**<0.001**	-0.636	-0.306
Everyday vs Less everyday	-0.363	0.065	-5.56	**<0.001**	-0.520	-0.206

Legend: SE= Standard Error; C.I.= Confidence Interval.

11.3. Premorbid Social Factor and Frequency of Cannabis Use

Regarding the Premorbid Social Factor (PSF), cases score worse in their premorbid social adjustment compared to controls (F (1,1691) = 81.4, p<0.001) and there is also a significant effect of cannabis use (F (2,1691) = 12.7, p<0.001) and an interaction effect between cannabis and group (F (2,1691) = 3.06, p=0.047).

Looking at multiple comparisons, corrected by Bonferroni, cases who never smoked cannabis are lower in premorbid social adjustment than cases less than everyday users (p=0.002) and everyday users (p<0.001) while there are no differences between these two groups (p=1.000). In controls, there are no differences in terms of sociability by frequency of cannabis use (all p>0.05).

Interestingly, there is also no difference between cases who smoked cannabis everyday and controls who never smoked cannabis in terms of sociability (p=0.225) and there are only modest differences between cases everyday users and controls everyday users (p=0.059) (**Table 36**) while all other differences between cases and controls remain significant (all p<0.001 – data not shown in table).

Table 36. ANOVA on PSF scores, corrected by Bonferroni.

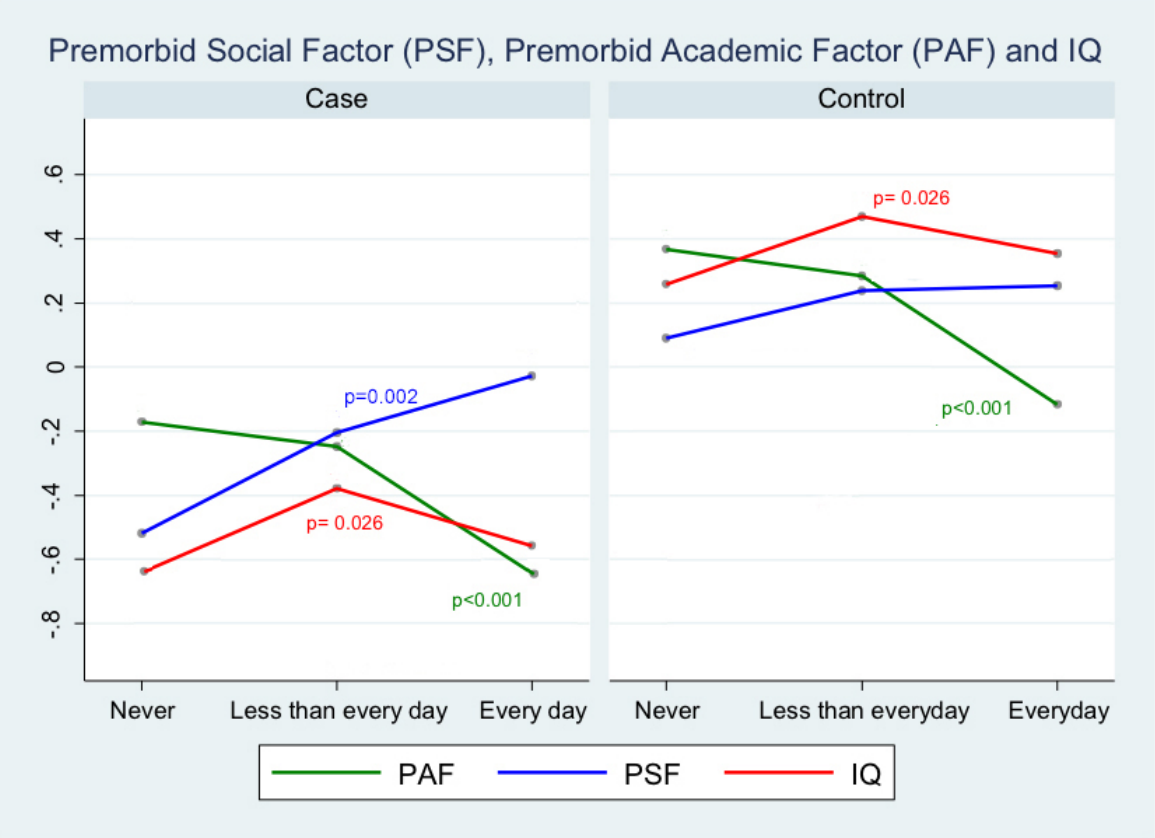
Variables	Contrast	SE	t-test	*p-value*	95% C.I.	
Controls E vs Controls N	0.164	0.119	1.38	1.000	-0.186	0.514
Controls E Vs Controls L	0.027	0.117	0.23	1.000	-0.318	0.373
Control L vs Control N	0.136	0.063	2.16	0.469	-0.049	0.323
Cases N vs Cases L	0.345	0.090	3.80	**0.002**	0.078	0.612
Cases E Vs Cases N	0.494	0.095	5.17	**<0.001**	0.213	0.775
Cases E vs Cases L	0.148	0.087	1.69	1.000	-0.109	0.407
Cases E vs Controls N	-0.206	0.084	-2.43	0.225	-0.455	0.042
Cases E vs Controls E	-0.370	0.128	-2.89	0.059.	-0.747	0.006

Legend: SE= Standard Error; C.I.= Confidence Interval. E=everyday; L=less than everyday; N=never.

11.4. Conclusions about Frequency of Cannabis Use on IQ, PSF and PAF

Figure 25 represents predicted values of premorbid school factor (PAF), premorbid social factor (PSF) and IQ, according with frequency of cannabis use in cases and controls. The higher IQ reported in both cases and controls who smoked cannabis in their lifetime is due to the subgroup of those who smoked cannabis less than everyday, thus accounting for the higher IQ reported in cannabis users overall. Both cases and controls who smoked cannabis less than everyday have a Premorbid Academic Factor (PAF) equal to people who never smoked cannabis, while the everyday users group accounted for the worse PAF reported in cannabis users. Controls show no differences by frequency of cannabis use in their sociability, while cases who smoked cannabis less than everyday or everyday had higher premorbid sociability scores (PSF) than never users.

Figure 25. IQ, PAF and PSF Scores by Frequency Of Cannabis Use in Cases and Controls.



Legend: these two graphs represent the predicted values of PAF, PSF and IQ in MANOVA, divided by cases and controls. PAF is represented by the green line, PSF is represented in blue and IQ is represented in red. On the Y axis are z-scores, on the X axis is represented the predictor "frequency of cannabis use".

In conclusion, the higher IQ recorded in cases cannabis recreational-users, is present in people who had a good premorbid social and academic adjustment before their 16 years, while in controls the better IQ of cannabis recreational users is only associated with a better academic adjustment before 16 years.

Everyday users were worse at school before 16 years, but they had better sociability and this was true in cases more than in controls, where this difference was not significant. Cases who never used cannabis were also the most impaired group in terms of sociability before their 16 years, despite their better premorbid academic adjustment, moreover they have the lowest IQ.

12. Exploratory Analyses

12.1. Other Drugs

Previous studies about cognition in psychotic cannabis using patients that did not exlude people with other substance abuse, have found similar results (i.e. better IQ and cognitive functions in drug users), and cannabis was confirmed as the preferred subsance (see meta-analisys by Potvin et al., 2008). However, given the large sample size, I wanted to explore other substance use and abuse. 103 subjects in total, of those who used other drugs (325 cases and 243 controls), declared to have abused of at least one of those drugs in their lifetime.

I wanted to perform again the MANOVA model with IQ, premorbid sociability (PAF) and academic adjustment (PSF) as outcomes, as already described, this time by excluding those subjects who have abused of at least one other drug in their lifetime. The results did not change, there was a significant interaction between cannabis use and group (Roy's Test $F(3,1595)=3.4$, $p=0.017$) due to PSF, that resulted higher in everyday and less than everyday cannabis users compared to never users, without any differences in control group. PAF of both cases and controls resulted worse in cannabis everyday smokers than in less than everyday users and never users. IQ was higher in less than everyday users in both groups.

Given that tobacco was suggested as a risk factor for psychosis (Gurillo, Jauhar, Murray, & MacCabe, 2015) it was also explored: a) tobacco use in the last 12 months (yes/no) was significantly related to cannabis use ($\chi^2(1)=287.7$, $p<0.001$) in both cases and controls; b) tobacco use (yes/no) was inserted, along with group (case/controls) in a MANOVA with IQ, PAF and PSF as outcomes where cases resulted lower in all scores (all $p<0.001$) and tobacco use in the last year was significantly related to higher premorbid sociability ($F(1,1635) = 24.8$, $p<0.001$), lower academic premorbid adjustment ($F(1,1635) = 53.1$, $p<0.001$) and lower IQ ($F(1,1635) = 25.9$, $p<0.001$), independently from group belonging; c) the same was true after excluding subjects with a lifetime cannabis-use from the sample; i.e. tobacco smokers resulted lower in IQ ($F(1,634) = 8.64$, $p=0.003$) and PAF ($F(1,634) = 15.9$, $p<0.001$) while the effect on PSF was mostly attenuated ($F(1,634) = 3.72$, $p=0.051$), without differences between cases and controls; d) number of cigarettes smoked in the last 12 months resulted higher in patients with a lifetime everyday cannabis-use (interaction $F(2,1781) = 12.8$, $p<0.001$).

12.2. Premorbid Adjustment in Childhood and First Adolescence

In order to explain my results in terms of neurodevelopmental impairment (Murray & Lewis, 1987), I wanted to look back at the Premorbid Adjustment Scale (PAS) and its scales (see Appendix V). Each of the 4 items of the PAS (a part from socio-sexual adjustment) is administered twice to the subject: by referring to his/her childhood (before 12 years) and to his/her first adolescence (between 12 and 16 years). Socio-sexual adjustment was excluded because it is not comparable at different ages. Thus, I performed again a PCA on PAS original reverse-scores, stratified by age (<12 years and 12-16 years). As expected, results were similar to the previous PCA performed on the nine scales, and clustered according to Kraiser's criterion on two principal factors, stratified by age (**Table 37**):

Table 37. Factor Loading after Rotation PAS <12years and 16 Years and New Factors.

Factor loading after rotation <12 years	Component	
	(PSF<12)	**(PAF<12)**
PAS Soc <12	**0.905**	0.122
PAS Peer <12	**0.891**	0.186
PAS Schol <12	0.053	**0.883**
PAS Adap <12	0.261	**0.803**

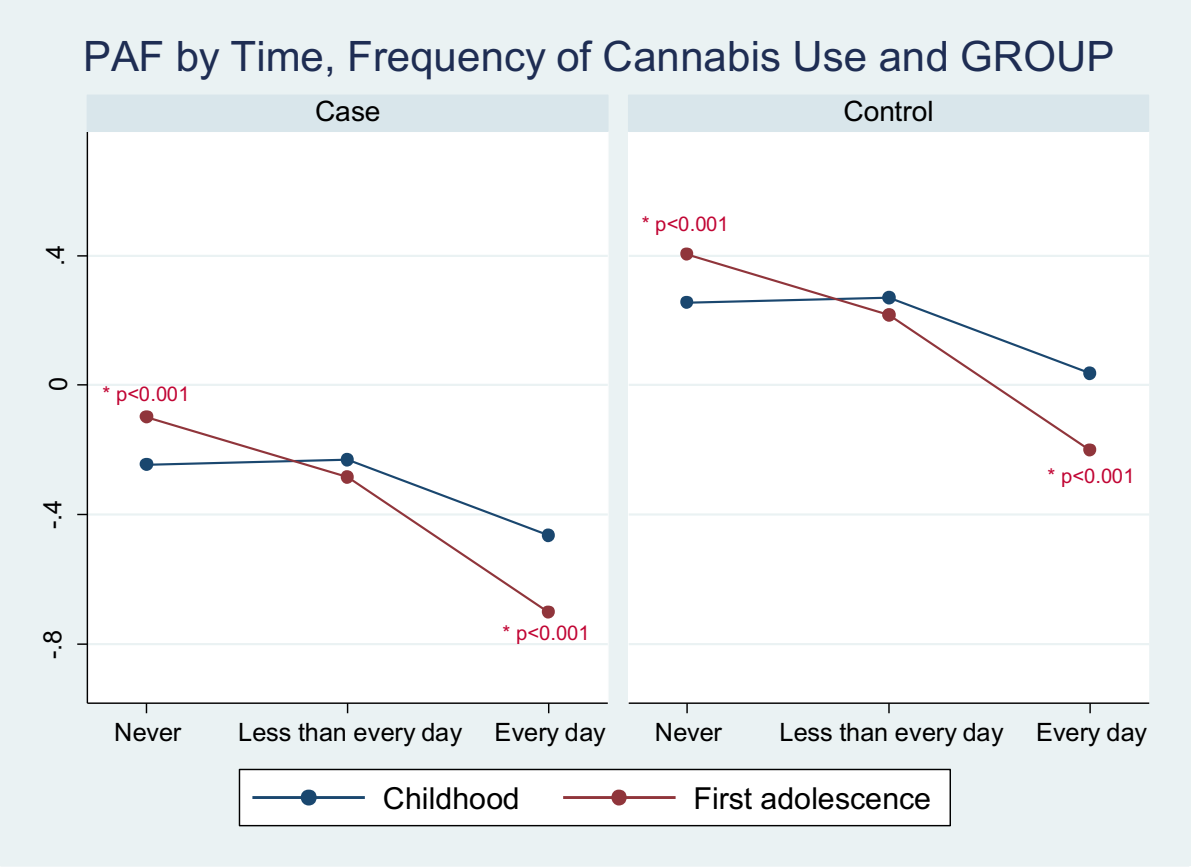
Factor loading after rotation 12-16 years	Component	
	(PSF 16)	**(PAF 16)**
PAS Soc 16	**0.910**	0.104
PAS Peer 16	**0.901**	0.148
PAS Schol 16	0.089	**0.874**
PAS Adap 16	0.154	**0.857**

A MIXED ANCOVA model was applied to study the difference on PAF and PSF between the two times of PAS, controlling for age, gender, ethnicity and Country.

I used group (case or control), time of PAS (<12 or 12-16 years) and frequency of cannabis use as independent variables, and a casual effect for id-patient was used to take into account the repeated measures (12 or 16 years) for each patient.

In premorbid academic adjustment (PFA), cases performed worse ($\chi2(1) = 141.29$, $p<0.001$) and there was a significant interaction between frequency of cannabis use and time of PAS ($\chi2(2) = 54.76$, $p<0.001$) (**Figure 26**).

Figure 26. Premorbid Academic Factor in Childohood and First Adolescence by Cannabis.



Legend: these two graphs rapresent the predicted values of PAF (Y axis), divided by cases and controls and by frequency of cannabis use (X axis). PAF<12 is rapresented by the blue line, while PAF-16 is in red.

That means, both cases and controls who never smoked cannabis in their lifetime, gained in their academic adjustment from childhood to early adolescence. Both cases and controls who later smoked cannabis sometime in their life stayed stable in their PAF, while cases and controls who became everyday smokers, had a drop in their PAF from childhood to first adolescence.

Table 38 shows multiple comparisons on this effect, for both cases and controls considered together, corrected by Bonferroni.

Table 38. MIXED MODEL on PAF Scores by Time. Cases and Controls. Corrected by Bonferroni.

Variables	Contrast	SE	z	*p-value*	95% C.I.	
Never-16 vs Never>12	0.146	0.030	4.83	**<0.001**	0.057	0.236
Less everyday-16 vs Less everyday>12	-0.052	0.028	-1.83	1.000	-0.137	0.031
Everyday-16 vs Everyday>12	-0.237	0.044	-5.31	**<0.001**	-0.368	-0.105

Legend: SE= Standard Error; C.I.= Confidence Interval.

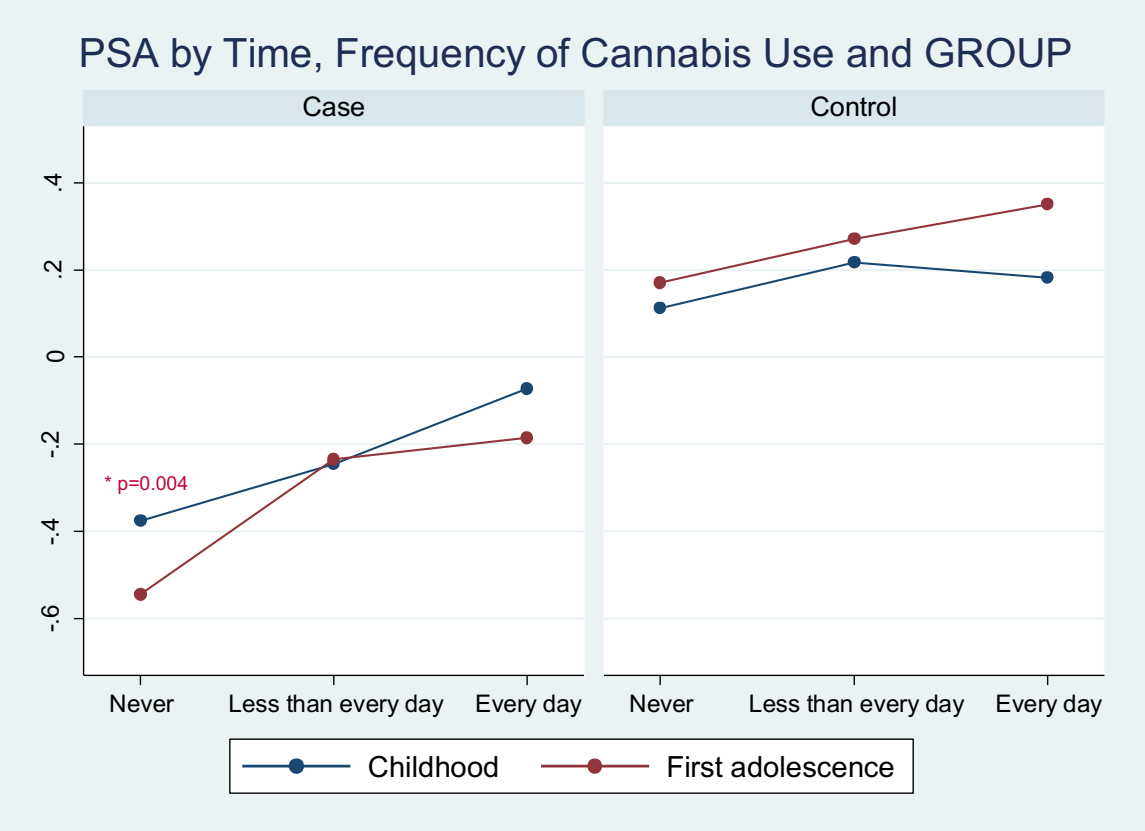
In premorbid social adjustment (PSA), cases had lower scores ($\chi2(1) = 92.3$, $p<0.001$) and the only group that had a significant drop in sociability from childhood to early adolescence was made of patients that never smoked cannabis in their lifetime (interaction effect between group, cannabis and age of PAS: $\chi2(2) = 7.5$, $p=0.024$).

Everyday cannabis smokers had a drop that became unsignificant after adjusting by Bonferroni (unadjusted p=0.016; adjusted p=0.241).

The opposite was evident in the control group, where everyday smokers gained in sociability in their early adolescence, but this difference became unsignificant after adjusting by Bonferroni (unadjusted p=0.045; adjusted p=0.669). Those who later would become recreational smokers (less than everyday group) were stable in their sociability either in case and in control groups. In conclusion, both cases and controls who later will smoke cannabis less than everyday are stable in their academic and social adjustment from childhood to early adolescence, while both cases and controls everyday smokers have a drop in their academic adjustment, but not in social adjustment.

Finally, both cases and controls who never smoked cannabis, gained from childhood to adolescence in their academic adjustment, but cases have a drop in their sociability (**Figure 27**).

Figure 27. Premorbid Social Factor in Childhood and First Adolescence by Cannabis use.



Legend: these two graphs represent the predicted values of PSF (Y axis), divided by cases and controls and by frequency of cannabis use (X axis). PSF<12 is represented by the blue line, while PSF-16 is in red.

Table 39 shows multiple comparisons of this effect.

Table 39. MIXED MODEL on PSA Scores by Time and Group. Corrected by Bonferroni.

Variables	Contrast	SE	z	*p-value*	95% C.I.	
Cases N-16 vs Cases N>12	-0.169	0.047	-3.63	**0.004**	-0.306	-0.032
Cases L-16 vs Cases L>12	0.115	0.043	0.27	1.000	-0.115	0.138
Cases E-16 vs Cases E>12	-0.113	0.047	-2.41	0.241	-0.250	0.025
Controls N-16 vs Controls N>12	0.059	0.035	1.70	1.000	-0.043	0.161
Controls L-16 vs Controls L>12	0.058	0.033	1.64	1.000	-0.043	0.152
Controls E-16 vs Controls E>12	0.168	0.083	2.01	0.669	-0.077	0.413

Legend: SE= Standard Error; C.I.= Confidence Interval. E=everyday; L=less than everyday; N=never.

2.3. IQ in Cases Who Smoked Cannabis Less than Everyday by Diagnosis

I started from the hypothesis that there exists a subgroup of patients with a recreational use of cannabis, who are less cognitively impaired at the onset and less socially withdrawn in their premorbid period than other patients and this was true in our sample of affective and non-affective psychotic patients.

At this point I wanted to have a look at first diagnosis attributed to the subjects at their admission, given that it was suggested that neurodevelopmental abnormalities are present in schizophrenia but not in bipolar disorders (Koenen et al., 2009; MacCabe et al., 2010) and that the latter show a much smaller premorbid deficit compared to schizophrenia (Trotta et al., 2015).

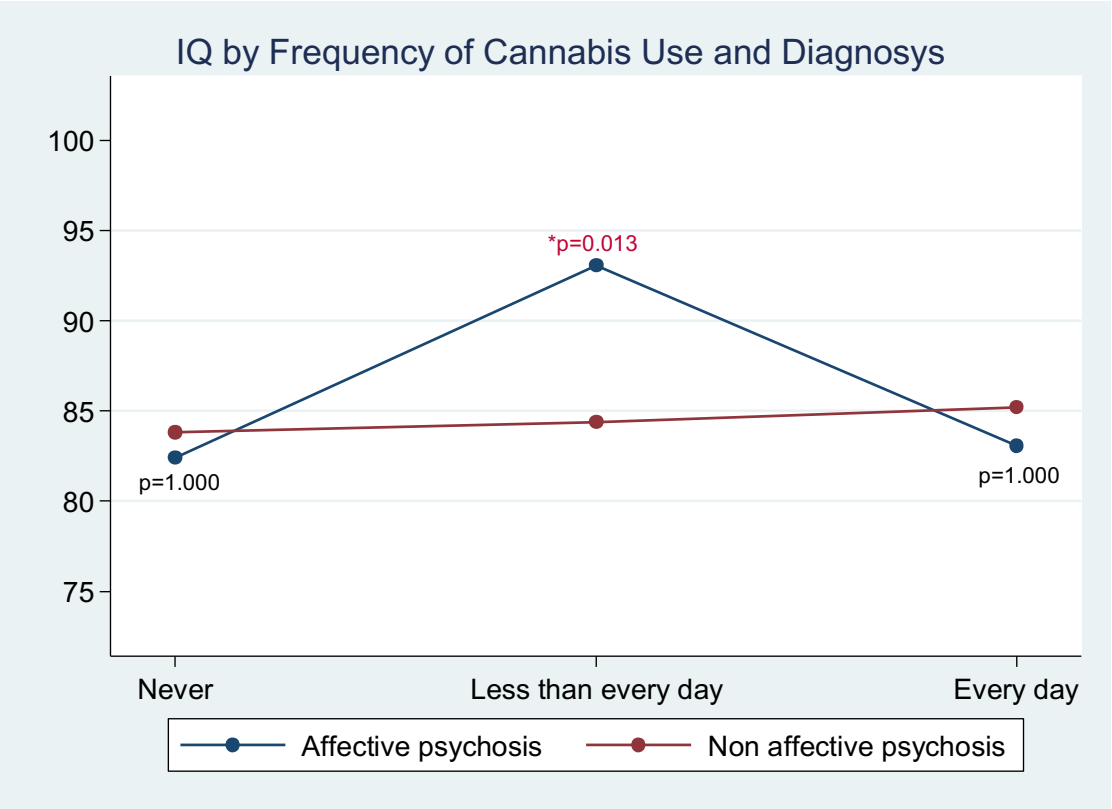
An ANOVA was performed on case group only with frequency of cannabis use (never/less than everyday/everyday) and diagnosis (affective/non-affective) as fixed factors and IQ as dependent variable.

The model was adjusted for Country, age, gender and ethnicity. Age was removed in the final mode because, as expected, resulted not significant within cases, given that in IQ calculation it is already taken into account. In this model, frequency of cannabis use was important in determining the IQ, in interaction with diagnosis (F (2,569) = 4.74, p=0.009).

That means, less than everyday users with affective psychosis were the only group with a higher IQ compared to their non-affective counterpart (p=0.013) and, within the group, compared to never-users group, both affective (p=0.020) and non-affective (p=0.010).

There were no differences in terms of IQ between affective and non-affective psychosis into the never-used group (p=1.000) nor into the everyday-user group (p=1.000) (**Figure 28**).

Figure 28. IQ of Cases by Frequency of Cannabis Use and Diagnosis.

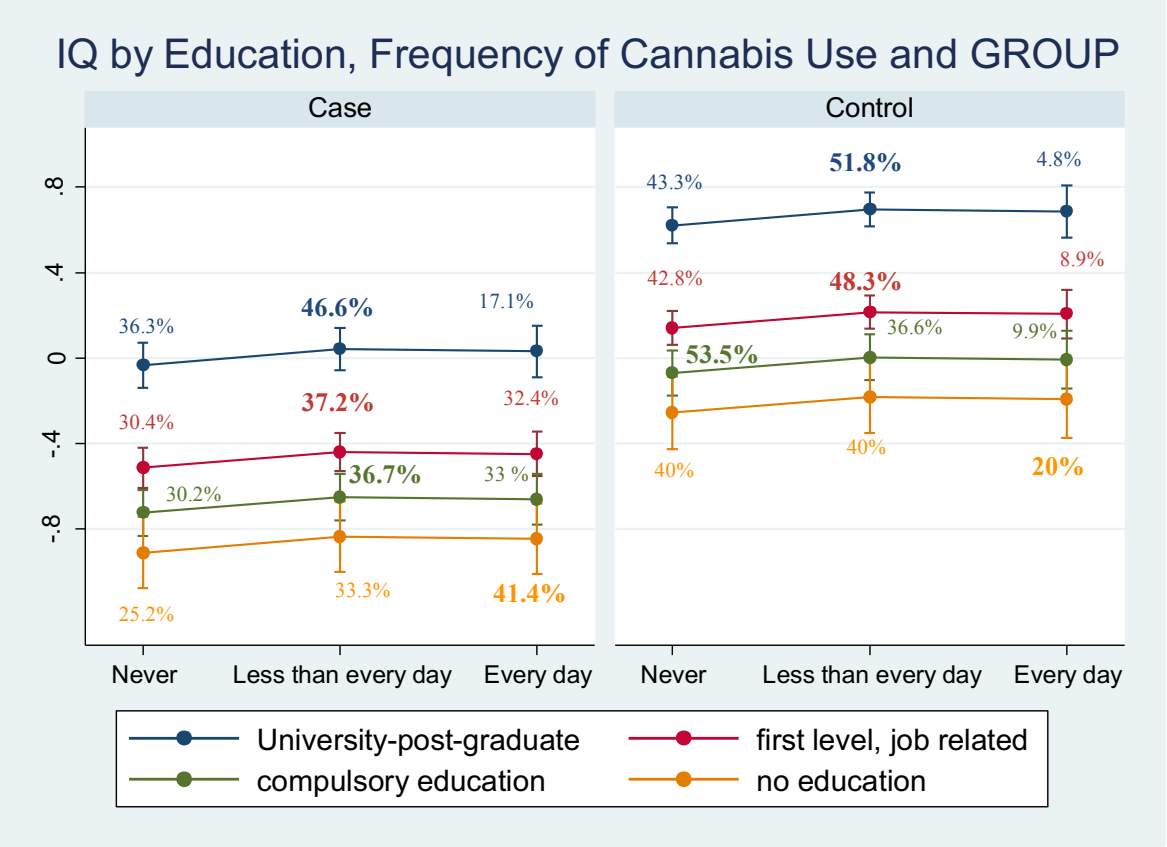


Legend: this graph represents IQ scores (Y axis) by frequency of cannabis use (X axis) by affective psychosis (represented in blue) and non-affective psychosis (represented in red).

12.4. Further Investigation on the IQ Model

a) Premorbid adjustment factors (PSF and PAF) were inserted as explanatory variables in the IQ model performed on the entire sample of cases and controls and social factor resulted not significant (p=0.582), while school premorbid adjustment was significantly related to IQ ($F(1,1692)=309.2$, $p<0.001$) but it did not entirely explain its variations in relation to cannabis use. In fact, both cases and controls with a recreational use of cannabis still resulted in significantly higher IQ than never users ($p<0.001$). By additionally correcting the analysis for education and occupation, they both were significantly related to IQ ($p<0.001$) and ultimately dissolved the cannabis effect on IQ ($p>0.05$). That means, IQ differences observed in cases and controls, in relation to cannabis use, are probably due to premorbid academic adjustment and successive educational attainment (**Figure 29**)

Figure 29. IQ of Cases and Controls by Frequency of Cannabis Use and Education.

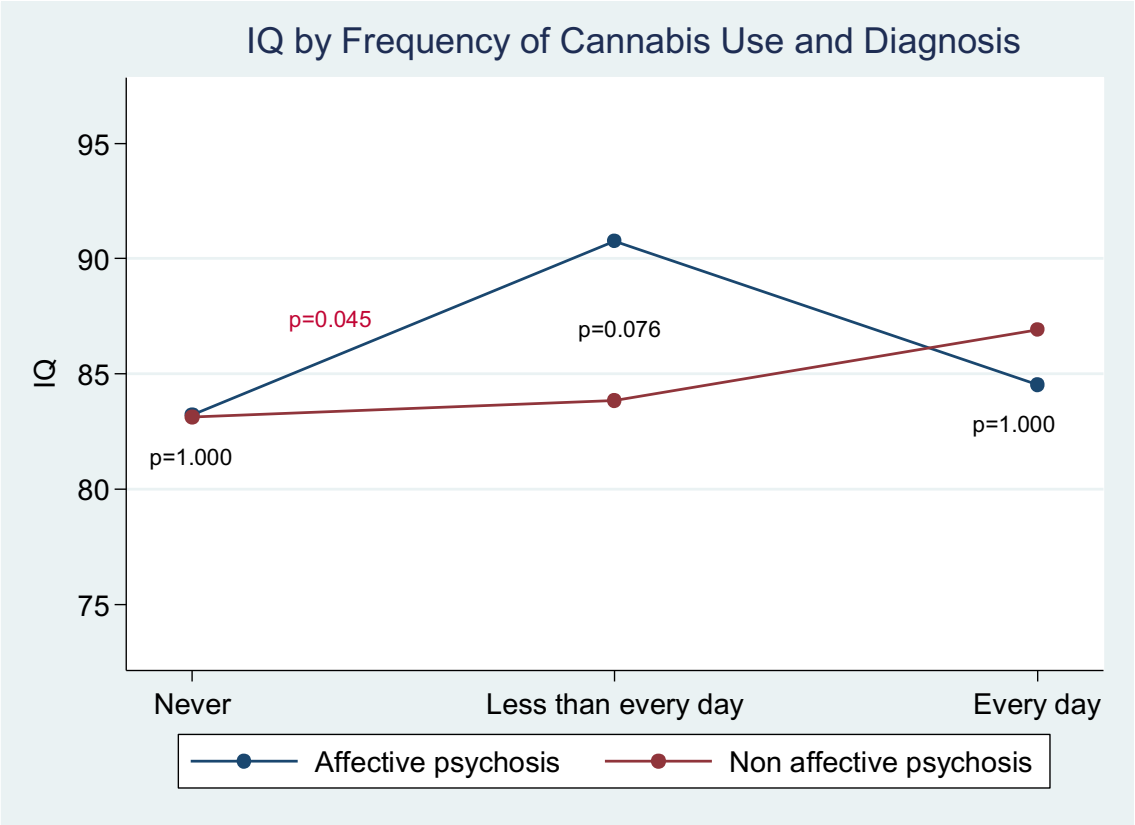


Legend: on the Y axis there are standardized values of IQ, corrected for age, gender, ethnicity, country, education and occupation; on the x axis are grouped subjects with different patterns of cannabis use. Percentages of cases and controls included in each category are also indicated.

b) The same analysis was applied on the above described IQ model performed on the basis of diagnosis and identical results were found: premorbid academic adjustment was significantly related to IQ (while sociability was not), but it did not explain the relationship between diagnosis and frequency of cannabis use in determining the IQ and cases recreational cannabis users with affective psychosis had still a higher IQ (p=0.027).

After adjusting this analysis for education and occupation, the difference between affective and non-affective psychosis in the less than everyday group became attenuated and unsignificant (p=0.076), but the interaction effect between frequency of cannabis use and diagnosis stayed significant (F (2,557) = 3.25, p=0.039) (**Figure 30**).

Figure 30. IQ by Frequency of Use and Diagnosis Corrected for Education.



Legend: this graph represents IQ scores (Y axis) by frequency of cannabis use (X axis) by affective psychosis (represented in blue) and non-affective psychosis (represented in red). The results are corrected for education

This was due to the fact that patients with affective psychosis who used cannabis less than everyday had a higher IQ, compared to patients with non-affective psychosis that never used cannabis (p=0.045). This suggest that these two groups are different in IQ for reasons that are not related to early scholastic adjustment and subsequent scholastic achievement.

c) WAIS full scale IQ was derived from four subtests that are also able to estimate some cognitive domains, described as follows (Taub & Benson, 2013):

- Block Design: Perceptual Reasoning;
- Arithmetic: Working Memory;
- Digit Symbol: Processing Speed;
- Information: Verbal Comprehension.

The four scales of WAIS were entered instead of IQ into the MANOVA (corrected by age, gender, country and ethnicity), without any correction of premorbid adjustment, in order to see if any of them have a higher influence in determining the IQ effect observed in relation to cannabis use.

Controls performed better in all scales, after correcting for potential confounders ($F(4,1712)=131.97$, $p<0.001$) and frequency of cannabis use influenced performance ($F(4,1712)=4.73$, $p<0.001$), as following described, without any significant interaction with group (p=0.113).

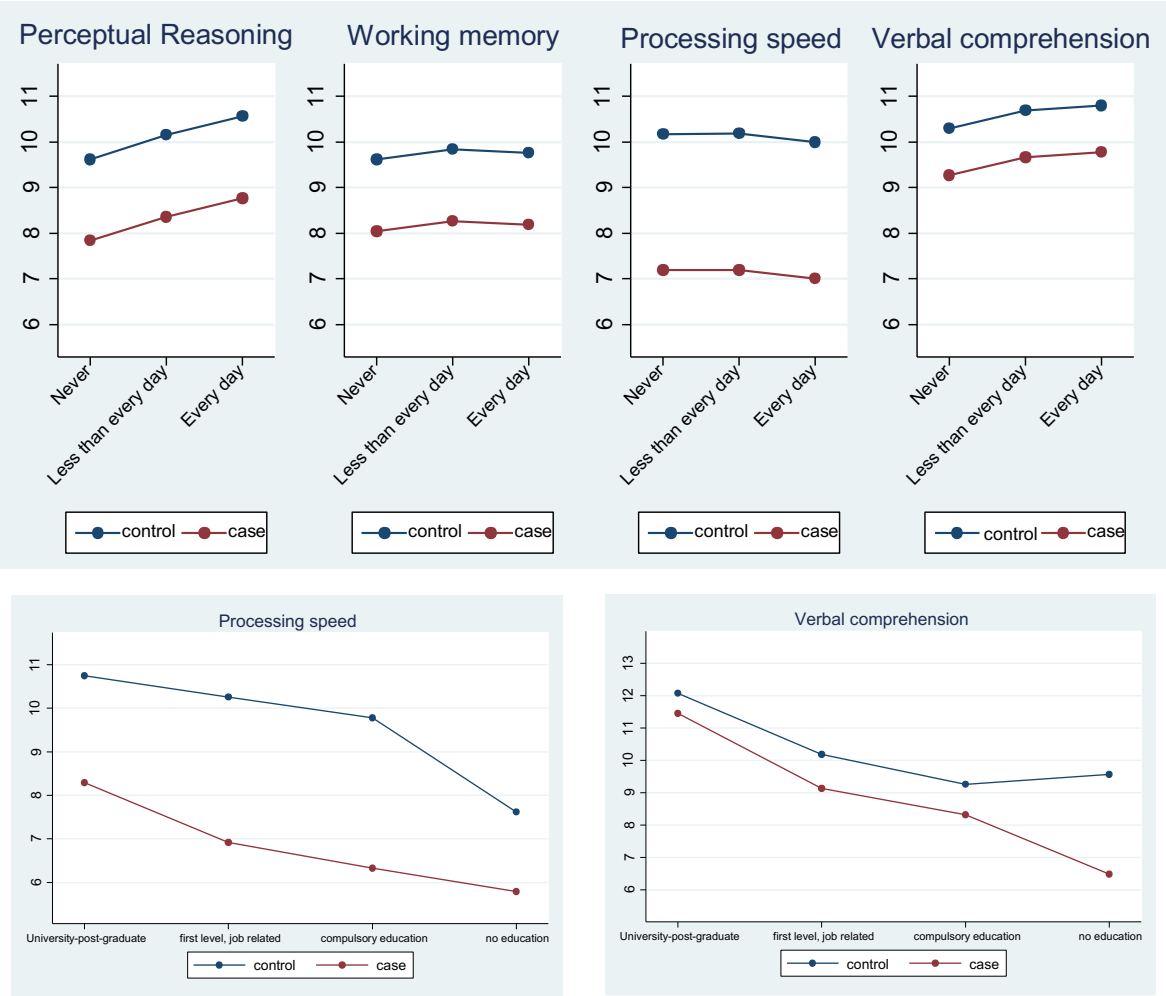
- **Perceptual Reasoning:** higher in cases and controls cannabis users, both everyday (p=0.002) and less than everyday (p=0.044).
- **Working Memory:** no differences in terms of cannabis use, taken alone.
- **Processing Speed**: a trend of worse performance in both cases and controls everyday users than in less than everyday (p=0.074).
- **Verbal Comprehension:** better in less than everyday users (p=0.007).

The analysis was further corrected by education and occupational status, and results stayed identical for Perceptual Reasoning that resulted still higher in cases and controls heavy (p=0.001) and recreational users (p=0.014).

There was an interaction effect between education and group in explaining both Processing Speed (p=0.012) and Verbal Comprehension (p=0.037), i.e. scores on these tests were better in controls with higher education but not in relation to cannabis use (**Figure 31**).

These results indicate that Perceptual Reasoning, that is also part of the measure of executive functions (Wechsler, 1981) could be important in determining differences between cannabis users and non-users, regardless education.

Figure 31. IQ Scales by Group and Frequency of Cannabis Use.



Legend: each graph on the highest part represents a different cognitive domain, which scaled scores are on the Y axis, by group (cases are in red and controls are in blue) and frequency of cannabis use (X axis).
The two graphs in the lowest part, represent Processing Speed and Verbal Comprehension scaled scores (Y axis) in relation to education (X axis).

12.5. What Does Augment the Risk to Smoke Cannabis?

The manova allowed me to describe the outcomes in terms of premorbid adjustment and IQ, given certain conditions of cannabis use, abuse or abstinence.

The IQ model was further designed with premorbid conditions and education as predictiors, because IQ results from a complex interaction of several aspects of an individual's trajectory. For the same reason, and following previous studies, it was also subsequently divided into the main four scales used in its calculation.

Given the complexity of the previous results, a multinomial regression was used in order to compare the risk to be everyday user or less than everyday user, rather

than never users, taking into account IQ scales, PAF and PSF as predictors, along with other variables (i.e. age, gender, ethnicity, country, education, and occupation).

In the final model, group belonging (p=0.161) became non significant in determining the ratio of the relative risk (RRR) to be a recreational cannabis user or an abstinent subject, i.e. the risk to approach cannabis in a recreational pattern of use was similar in cases and controls, while group stayed significant in determining a higher risk to be an everyday user (RRR=3.6, p<0.001, CI 95% 2.38, 5.56), i.e. cases were 4 times more likely to be heavy cannabis users than controls.

Holland presented a two-fold increased risk to have everyday smokers than abstinent subjects (RRR=2, p=0.005, CI 95% 1.23, 3.32), thus confirming previous descriptive statistics.

Males were up to 2.6 fold more likely to be heavy cannabis smokers (p<0.001, CI 95% 1.85, 3.79) and 1.6 more likely to be recreational smokers (p<0.001, CI 95% 1.23, 2) than abstainers in both the case and control group.

Unemployed people were 2 fold more likely to be heavy cannabis users than abstainers (RRR=2.2, p<0.001, CI 95% 1.52, 3.14), but this condition did not influence the probability to be recreational users (p=0.449). People with a compulsory education were less likely to be recreational smokers than people with a university degree (p=0.021).

The risk to be a recreational user augments with higher scores of Verbal Comprehension (RRR=1.1, p=0.016, CI 95% 1, 1.08) and Perceptual Reasoning (RRR=1.1, p=0.002, CI 95% 1.02, 1.10).

Even if higher scores in perceptual reasoning and a higher premorbid social adjustment, taken alone, augment the risk to be a recreational user, if they both are higher in the same subject ultimately reduce this risk (OR=0.96, p=0.017, CI 95% 0.92, 0.99).

Everyday use is predicted by higher scores of Perceptual Reasoning (RRR=1.1, p>0.001, CI 95% 1.06, 1.18) and Verbal comprehension (p=0.022), the latter in interaction with a higher sociability (OR= 0.94, p=0.009, CI 95% 0.89 0.98) and lower scores in Processing Speed (RRR=1.1, p=0.022, CI 95% 1, 1.1), the index less related to general IQ (Taub & Benson, 2013) but this latter effect is moderated

by higher levels of premorbid academic adjustment that reduce the risk of cannabis heavy use in people with lower scores of processing speed (RRR=0.9, p=0.009, CI 95% 0.85, 0.98).

A higher working memory (RRR=0.9, p=0.008, CI 95% 0.88, 0.98) moderates the role of a higher premorbid sociability in increasing the risk to be a heavy cannabis user, acting as a protective factor in more sociable people.

12.6. What Regulates the Risk to Became a Recreational or an Everyday Cannabis User?

We know that levels of THC in the cannabis used, age at first use and current use could be important in studying the relationship between the variables of this Study (Di Forti et al., 2007; Schoeler & Bhattacharyya, 2013).

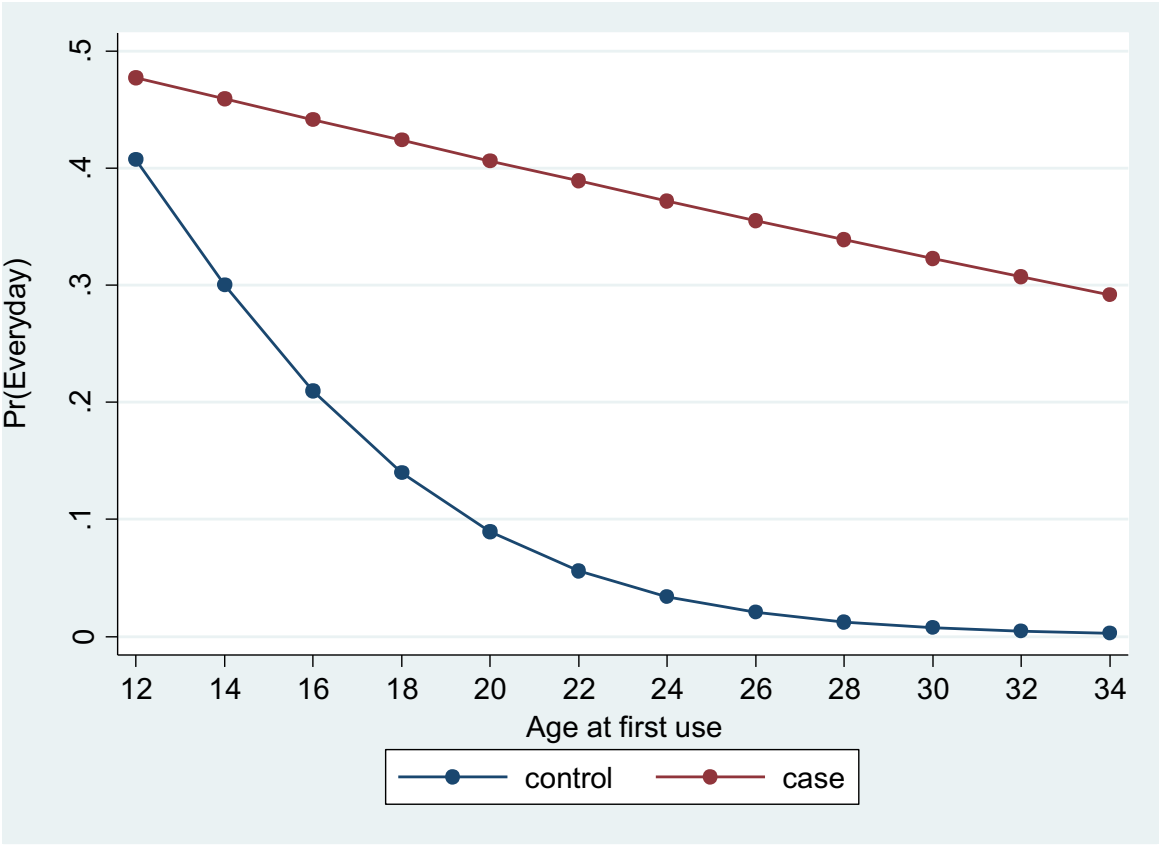
In our previous study (GAP sample), we did not find any relationship between age at first cannabis use, current use, type of cannabis used and IQ or premorbid IQ, probably due to the small numbers of the sample. In my opinion, the best way to look at them is in the role that they have in determining the risk to be users and recreational users, along with other variables of interest.

As an exploratory analysis on these other variables, a logistic regression was computed, using frequency of cannabis use (only two categories) as an outcome variable in order to estimate the risk to be an everyday user or a less than everyday user, taking into account a list of predictors (age, gender, country, ethnicity, education, occupation, age at first use, % of THC, current use, PSF, PAF and the four scales of WAIS).

In the final model, country, gender, age, ethnicity and current cannabis use were not significant and were subsequently excluded them from the analysis. The risk to be an everyday smoker was higher for cases, in interaction with age at first use, i.e. while the risk of controls diminishes when age at first use increases, this is not true for cases, whose risk stay higher even when age at first use increases (OR=1.2, p=0.001, CI 95% 1.09, 1.45).

The highest risk was for cases who smoked cannabis earlier in their life (see **Figure 32**).

Figure 32. Probability to Be Everyday Cannabis User by Age at First Use and Group.



Legend: on the Y axis is represented the probability to be an everyday smoker, while on the X axis are represented different ages at first cannabis use for cases (in red) and controls (in blue).

THC absolute concentration >10% augmented almost 2 folds the risk to be an everyday smoker (OR=1.8, p=0.001, CI 95% 1.29, 2.60), and was not in interaction with any other variables.

As already observed in previous analysis, unemployed people were more likely to be everyday users than recreational users (OR=1.9, p<0.001, CI 95% 1.40, 2.84).

A higher premorbid social adjustment (OR=1.6, p=0.019, CI 95% 1.08, 2.60) and lower premorbid academic adjustment (OR=0.8, p=0.040, CI 95% 0.68, 0.99) increased the risk to be a heavy cannabis user, along with having completed compulsory or first level education or having no education (all p<0.05), compared with university degree.

Interestingly, higher scores of working memory moderate the role of sociability and education. So, even if both having an intermediate level of education and being more sociable before your 16th year increase the risk to be a cannabis heavy user rather than a recreational user, higher scores of working memory reduce this risk in more sociable people (OR=0.9, p=0.021, CI 95% 0.90, 0.99) and in people who completed compulsory school (RRR=0.7, p=0.012, CI 95% 0.62, 0.94) and achieved a diploma (RRR=0.8, p=0.005, CI 95% 0.67, 0.93).

Chapter 6

Analysis and Discussion of the Findings

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1. Introduction

In this chapter I will summarize the key finding of this thesis. I am going to comment on the results, by comparing them with the literature on this topic. I will address methodological issues, strengths and limitations of the study and I will suggest how my findings might contribute to the field of research into psychotic disorders. Finally, conclusions of the study will be displayed.

2. Hypotheses

2.1. Confirmatory Hypothesis

1. I expected that cases would show a greater cognitive impairment (i.e. lower IQ) than controls overall, independent of potential confounders and across all countries.
2. I expected that cases would be more socially and academically impaired in their premorbid period than controls overall, independent of potential confounders and across all countries.
3. I expected that cases would be more likely to have smoked high potency cannabis, starting at an earlier age and with a higher frequency than controls.

2.2. Replication-Hypothesis

I expected that cases who have used cannabis in their lifetime would be less cognitively impaired (i.e. higher IQ) than those who did not, independent from potential confounders.

2.3. Original Hypotheses

1. I expected that patients who used cannabis in their lifetime would show a better premorbid adjustment.
2. I expected that "Country" significantly would affect the relationships between the variables of interest.
3. I expected to find better premorbid adjustment (both social and academic) in cases who smoked cannabis in their lifetime "less frequently than everyday", compared to people who smoked cannabis "everyday" and to people who did not smoke cannabis at all in their lifetime. I hypothesized the existence of a subgroup of patients with a recreational use of cannabis, who are less cognitively impaired at the onset and less socially withdrawn in the premorbid period than other patients.

3. Findings

The final sample of the study included 1,895 subjects 834 cases and 1,061 controls), from different Countries. All differences between cases and controls in age, gender distribution, ethnicity, education, occupation, and relationship status were expected, as being male (Aleman et al., 2003; McGrath et al., 2004) unemployed, single and having poor education have been associated with an increased risk of psychosis (C Morgan et al., 2008; Stilo et al., 2013). Differences in age, are due to the fact that psychosis is a psychiatric disorder that shows a peak of incidence in young females (29-32 years) and even younger males (20-24 years) (Castle, Sham, & Murray, 1998) that are also overrepresented in case group. Males

in case group are younger (i.e. have an earlier age of onset) than females (exploratory analysis $t(831)=-5.8$, $p<0.001$), but this is not true in control group ($p=0.337$). Indeed, the control sample was recruited in order to be representative of the general population than matched with case group.

A difference with previous findings on UK samples (C Morgan et al., 2008; Stilo et al., 2013), was represented by living status. In fact, our cases were less likely to have ever lived alone in their lifetime than controls and they were more likely to live with their parents or in other families. This difference could be due to the inclusion of countries different from UK (for example Spain and Italy) where young people (18-34 years) have been more likely to increasingly live with their parents over the last years (EUROSTAT, 2016) probably due to the economic crisis and/or to their cultural background, e.g. by exploratory analyses on our sample we know that 36.9% of cases and controls in Spain are living with their parents (45.5% with parents, other family or institutions) vs. 8.3% who are living alone and 37.9% of cases and controls in Italy are living with their parents (50.6% with parents, other family or institutions) vs. 9.5% who are living alone. According to the Eurostat report (2014) Spain and Italy have a higher proportion of unemployed people among young adults (18-34 years), who are also living with their parents, compared to UK (EUROSTAT, 2014) and the unemployed condition is overrepresented in our case group and this could be another reason for this difference in living status.

As expected, cases showed a lower IQ than controls overall, independent of potential confounders and across all countries (Bora et al., 2010; Matheson, Shepherd, Laurens, & Carr, 2011; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; Zanelli et al., 2010). They were also more socially and academically impaired before their 16 years than controls, independent of potential confounders and across all countries (Cannon et al., 2001; Hans et al., 1992).

Cases in our sample were also more likely to have used cannabis in their lifetime compared to controls (68.4% vs. 55.7%) and 24.3% of cases were currently using cannabis, a higher percentage compared to controls (13.3%), but lower than that referred in Myles and colleagues' meta-analysis (33.3%) (Myles et al., 2016). This difference could be due to the period of the recruitment and assessment (from the 1st

of May 2010 to 30th of June 2015), given that rates of cannabis use show geographical variations and a modest decline in the last years, after a peak prevalence between 1995 and 2000, in psychotic patients (Myles, Myles, & Large, 2016).

I also confirmed expected data on pattern of cannabis use, i.e. males were more likely to smoke cannabis overall (Donoghue et al., 2014; Larsen et al., 2006; Sevy et al., 2010), cases were more likely to have smoked high potency cannabis, starting at an earlier age and with a higher frequency than controls (see also Di Forti et al., 2009) and this effect was mostly attributed to tolerance induced by the substance.

3.1. IQ in Cannabis Using Patients and Controls Across Europe

I have tried to replicate on the EU-GEI sample previous findings on IQ described in Chapter 4.

The role of other illegal drugs of abuse was ruled out in an explortory analysis where subjects with at least one drug of abuse in their lifetime were removed from the sample and the analysis were repeated, without any change in main results.

Tobacco use in the last 12 months, in our sample, was related to a higher premorbid sociability, a lower premorbid academic adjustment and a lower IQ. This latter finding suggests that, in spite of the relationship between cannabis and tobacco use, cannabis users and tobacco users are not coincident in their cognitive characteristics, but merely in premorbid predisposition to substance-use and it is not surprising. However our data on tobacco-use were limited to recent pattern of smoking (i.e. in the last 12 months), thus it was not possible to go in depth of this association.

Both patients and controls who smoked cannabis in their lifetime had a 2.02 points higher mean IQ than their respective no-cannabis group and the analysis was corrected for age, gender, ethnicity and also occupation and education, in order to rule out the possible confounder of premorbid conditions influencing current IQ trough socio-economic status (Barona et al., 1984; Crawford & Allan, 1997).

In line with previous meta-analysis (Yücel et al., 2012; Potvin et al., 2008; Rabin et al., 2011), first episode psychotic patients that used cannabis in their lifetime showed a better IQ overall, thus replicating our previous findings on the GAP sample (Ferraro et al., 2013).

This time, however, controls who reported to have smoked cannabis in their lifetime showed a higher IQ than no-cannabis control group and, to date, this is the first study that found a higher current IQ in healthy cannabis-users.

Previous studies on subjects from the general population suggest no effects of cannabis on current cognition after 25 days of abstinence or a small residual detrimental effect, before this period (Schreiner & Dunn, 2012, Grant et al., 2003). Moreover, results from the Dunedin longitudinal cohort study show that subjects with more persistent cannabis dependence present an IQ decline over time, when compared to study members who never used cannabis, an effect not observed in previous meta-analyses (Meier et al., 2012). On the other hand, it was suggested an association between higher childhood IQ and subsequent cannabis recreational or discontinued use in adolescence (Ensminger et al., 2002; Fleming et al., 1982; Kellam et al., 1980; White & Batty, 2012; White, Gale, et al., 2012; White, Mortensen, et al., 2012) and subjects in the Dunedin study who reported a lifetime recreational use of cannabis, but not dependence, started with a higher IQ than those that never used cannabis and had a similar IQ at their 38 years (Meier et al., 2012).

Thus, there are no reasons to sustain that the higher IQ detected in controls who used cannabis in their lifetime is subsequent to an ameliorative effect of the substance and it is more likely that it is due to better premorbid conditions, e.g. better IQ before cannabis use has started. The difference in IQ in control group could have been also identified thanks to the big proportion of the sample and to the differentiation and heterogeneity across different Countries. In fact, the difference in IQ was small (2.02 points) and lower than the established standard deviation of the WAIS (±3), thus suggesting a role of the sample size in detecting it. Additionally, we had the opportunity to look at an heterogeneous sample, different in terms of ethnicity distribution and socioeconomic status by country and able to overcome most of the selection bias (Heckman, 1979), some of which could have

been also implicated in previous studies like the abovementioned Dunedin Cohort Study (Gonzalez & Swanson, 2012).

The factor "Country" resulted significant as a main effect but not in interaction with cannabis or group, i.e. across countries, IQ resulted similar in relation to cannabis use and group but shifted. In an exploratory analysis, the IQ shifting resulted from interactions between country and age, ethnicity, education and occupation, i.e. some cities included in different countries have more ethnic variation, are more educated, have different occupational conditions and are definitely "younger" than others, thus statistically indicating the importance of these variables in influencing IQ in different cultural contexts and the extraordinary opportunity offered by a cross-country design, able to recruit a sample tested with the same instruments (differently from meta-analytic samples) that stays heterogeneous even after a statistical correction for these variables.

3.1. Premorbid Adjustment in Cannabis Using Patients and Controls Across Europe

In order to look at premorbid adjustment, I first confirmed through the factorial analysis the structure of PAS and its suddivision in a Premorbid Social Factor and a Premorbid Academic Factor, the latter being a proxy for premorbid IQ (Barajas et al., 2013; Norman et al., 2005).

Both cases and controls who smoked cannabis in their lifetime started with a lower premorbid academic adjustment, that was previously indicated as a predisposing factor for cannabis use (Wills, Walker & Resko, 2005) and was already observed in several studies on subjects from the general population (Apantaku-Olajide, James, & Smyth, 2014; Krohn, Lizotte, & Perez, 1997; Meier, Hill, Small, & Luthar, 2015; Lee, Winters, & Wall, 2010). In the previous GAP study, Premorbid IQ was estimated using the *Wechsler Test of Adult Reading* (WTAR), a reading test normed with the WAIS-III, which is able to provide a broad estimate of general ability before the illness (Holdnack, 2001) and results a pure measure of premorbid intelligence, strictly related to current IQ and different from

premorbid school adjustment (including both academic achievement and adaptation at school) that could be influenced by other factors independents from IQ.

Nonetheless, this finding seems to be counterintuitive in relation to the higher IQ of cannabis-using subjects, given that these two measures (IQ and PAF) are related each other. Kandel (1978) has found similar results, that poor school performance is a common antecedent of substance use but substance use is positively related to a higher IQ. An analogous finding was reported by Legleye and colleagues (2010) who revealed also that adolescents who only experimented with the use of cannabis, without changing to subsequent daily use, were less likely to drop out of secondary school than adolescents who never used cannabis and they highlighted that the odds of dropping out increased with the frequency of use beside early cannabis use. This issue was addressed in the final model stratified by frequency of cannabis use.

Differences in sociability were not significant in controls in relation to cannabis use, while first episode psychotic patients who used cannabis showed better premorbid sociability before 16 years than patient who did not, in contrast with a previous study that did not find such effect (Leeson, Harrison et al., 2011).

It is possible to speculate that the relationship between cannabis use and premorbid sociability was different in cases and controls for at least two reasons: a) PAS is a test specifically designed for assessing premorbid conditions in psychosis and could be more sensitive to differences in this subgroup of people, in fact social adjustment factor alone is able to explain most of the variance of the premorbid adjustment in childhood and early adolescence in the case/control group; b) healthy controls, that are generally not pathologically impaired in sociability, present a small but not statistically detectable difference ($p=0.053$) of this aspect in relation to cannabis use, i.e. healthy people who do not smoke cannabis are not socially withdrawn, they are probably involved in different peer environments, not predisposing to drug-use initiation (Bauman & Ennett, 1996; Vervaeke et al., 2008). As hypothesized, given that premorbid sociability is the most impaired domain among affective and non-affective psychosis (Norman et al., 2005), this finding suggests a lower premorbid predisposition of this group to psychosis.

The factor “Country” resulted significant as a main effect in all these analyses but not in interaction with cannabis use, i.e. academic and social adjustment resulted similar in relation to cannabis use, but shifted in different Countries. The only difference by country (i.e. the shift), accounted for group and ethnicity, i.e. cases in Holland were better in their premorbid academic adjustment and closer to control group than other cases. Controls in Spain were better in their social adjustment than other countries and very different from respective cases. In some countries, minority Ethnicities revealed a better adjustment before their 16, e.g. in Holland and Spain they shown a better early sociability compared to white people and this could be related to a different early cultural environment, while in Italy they had a better premorbid academic adjustment, compared to minority Ethnicities from other countries, opposite to finding from other studies (G. Bhattacharyya, Ison, & Blair, 2003) and this is probably due to the fact that, in Italy, they are mostly first generation migrants (100% of black people and 90.5% of other ethnicities are migrants), so they are referring to school adjustment in their original country.

3.2. Is Frequency of Cannabis Use Lifetime of Crucial Importance in Relation to Premorbid Adjustment and IQ?

As already mentioned, longitudinal studies on IQ and cannabis use have found a relationship depending on frequency of cannabis use, that means, between higher premorbid IQ and school adjustment and later recreational or discontinued use, though a lower premorbid IQ resulted as a predictor for regular or heavy cannabis use (Ensminger et al., 2002; Fried et al., 2002; Meier et al., 2012; White et al., 2012; White & Batty, 2011; Kellam et al., 1980). Other important variables of interest are THC concentration in the cannabis used, age at first use (Di Forti et al., 2007; Yücel et al., 2012) and current use (Pope, 2002).

However, none of these variables, taken alone, is sufficient in explaining the potential harmful effect of cannabis without any indication of the frequency of its use, that is the estimated amount of the substance and the dependence-behaviour. E.g. we cannot have any information from recent-use, THC concentration or age of

first use if the substance was used just once or twice. Thus, “frequency of use” is a superordinate category and the stratification of the sample by a combination of these abovementioned variables (see for example Fried et al., 2002, 2005) would be a forced interaction strategy in looking at outcomes, that additionally risks to reduce the power of each observed condition, thus decreasing the probability to detect little differences. Instead, I decided to perform logistic models in order to look at the relationship between these variables and the risk to became heavy cannabis users.

High frequency of use lifetime (everyday cannabis use) was predicted by an earlier age at initiation, especially in controls, and as a result of the selection of High Potency Cannabis (THC absolute concentration >10%). Current use was not related to frequency of cannabis use. Two further exploratory analysis were performed on this variable and their results are briefly described at this point of the work: a) as expected, once entered as fixed factor with current or not-current use in a MANOVA, were never users were excluded, frequency of use was able to predict IQ, PAS and PSF scores within cannabis users ($F(3,1032)=10.30$, $p<0.001$), while current use was not ($p>0.005$); b) in a MANOVA where current use was inserted alone and never users were codified as the baseline category (i.e. never used/ used but not currently/ currently use) patients and controls with current cannabis use were not different from abstainers counterparts in any of the outcomes ($F(3,1028)=0.14$, $p=0.937$) nor in interaction with group, so the lack of difference was present in both case and control group ($F(3,1029)=1.92$, $p=0.125$).

However, it is not possible to give a definitive statement about acute or residual toxicity of cannabis starting from these results. In fact, the selected sample of cannabis smokers included abstinent and not abstinent users in this study. The cut-off for current use was 12 months and, as a consequence, the group of current users included people that could suffer from residual effects, mixed with a proportion of people who last smoked cannabis more than 28 days before the assessment, thus not suffering of such effect (Pope et al., 2002). On the other hand, frequency of use referred to the period in which cannabis was mostly used in the lifetime.

Thus, our frequency and current-use variables are more “behavioural indexes” and indicators of the amount of cannabis intake in a certain period of life, rather

than acute and current “intoxication indexes” (see also Schnakenberg Martin et al., 2016).

In the next paragraphs, I will summarize and comment on the results obtained by examining frequency of cannabis use. 1,739 subjects were included in the final analysis looking at relationships of group and frequency of cannabis use with premorbid conditions and IQ and the interaction between these variables resulted significant in determining the outcomes, as following described.

3.2.1. Never Users

As expected, cases in this subgroup performed significantly worse in IQ scores than recreational cannabis users (Ferraro et al., 2013; Yücel et al., 2012; Potvin et al., 2008; Rabin et al., 2011) and similarly to everyday users. The lack of difference in IQ between cases everyday users and never users was already found in previous studies (Joyal et al., 2003; Pencer & Addington, 2003; Sevy et al., 2007). The novelty of this result consists in having compared the three groups at the same time by matching them with their healthy control counterparts.

The same IQ difference was detected between abstainers and recreational users in healthy controls and will be discussed in the following part.

As expected, cases, but not controls, showed a poorer premorbid social adjustment, compared to both recreational and heavy cannabis users. Similar results were also incidentally found by Sevy et al., (2010) and Compton et al., (2011).

Interestingly, this group of patients was the most impaired group in terms of sociability and had a further drop in sociability from childhood to early adolescence, in line with the neurodevelopmental hypothesis (R. Murray, O’Callaghan, Castle, & Lewis, 1992; R M Murray & Lewis, 1987). It was also suggested that a poor premorbid social adjustment is more often related to an insidious onset and later age of onset (Bailer et al., 1996), as is the case in our sample.

Both cases and controls that never smoked cannabis had a higher academic adjustment before their 16th year compared with cannabis users (see also Sevy et al., 2010; Compton et al., 2011). However, both groups presented a gain in their

scholastic adjustment from childhood to early adolescence. In this gain, the role of gender and diagnosis, for cases, were controlled and therefore excluded.

While this could be intuitive for controls, it seems in contrast with previous results on premorbid academic adjustment in psychosis, that is normally considered impaired and in further decline from childhood to late adolescence (from 16 years) (D. N. Allen et al., 2013; Strauss et al., 2012) and was proposed as related to the genetic risk for schizophrenia (Walshe et al., 2007). However, we do not know if the gain continues in late adolescence or if, after a normal phase between childhood and first adolescence these subjects will show a decline in academic adjustment. We can imagine that it happens after their 16 years, because their IQ is the lowest between sub-groups of cases and similar to IQ scored in everyday cannabis users, that have instead a drop in premorbid academic adjustment from childhood to early adolescence.

Looking at education, almost 41% of cases that never used cannabis achieved a diploma, but they were still mostly unemployed; and 42% of them had a partner at the moment of the interview, but they mostly lived with their parents at the onset.

Age of onset of psychosis is another important point of interest in explaining this difference. In fact, this subgroup had significantly later age of onset and greater variance (34.8±12.1), compared with recreational cannabis users (29.1±9.3) and heavy cannabis users (26.8±7.7) and they were predominantly females (57%). In support of this consideration, a recent study, that divided a large cohort of schizophrenics into non-users, subjects with a lifetime history of cannabis use or dependency, found no differences in premorbid cognitive ability after controlling for age at onset of illness and socio-economic status (Power et al., 2015).

A correlation between higher academic adjustment in childhood - but not in early adolescence - and later age of onset was found by Monte, Goulding and Compton (2008), along with lower social adjustment in early adolescence, as is the case in our sample. Nevertheless, their sample included 45.3% of patients with a cannabis abuse disorder and they did not divided or controlled for this variable (Monte et al., 2008). In my opinion, this could have nulled the possibility to look at this relative

gain in early adolescence, given that cannabis users have a drop in premorbid academic adjustment.

It is possible to speculate that this subgroup of abstinent patients, has a drop in its academic adjustment in late adolescence, i.e. after 16 years, close to the onset of the prodromal phase (Allen et al., 2013; Monte et al., 2008; Strauss et al., 2012) but not before, while social adjustment is impaired from childohood and has a drop in early adolescence, as expected (Sevy et a., 2010; Compton et al., 2011).

Horton and colleagues (Horton, Tarbox, Olino, & Haas, 2015) show something similar in a graph enclosed in their recent study i.e. a little gain in academic premorbid adjustment in early adolescence, that was not statistically explored in its significance, followed by a drop in late adolescence, in a group of first episode psychotic patients that they defined with a stable-poor functioning. However, they did not look at cannabis use lifetime and just excluded patients with any substance abuse in the last 6 months. Authors who specifically linked the higher social deterioration with a later onset of psychosis and the higher academic deterioration with an earlier onset, divided these two conditions into the notion of Deficit or Not-Deficit Syndrome, the first being predictive of a higher severity of negative symptoms (Galderisi et al., 2013; Rabinowitz et al., 2002).

Even if Kirkpatrick et al. (1996) have initially identified a less severe prevalence of lifetime cannabis use in deficit compared to non deficit syndrome, but no differences in terms of current use (Kirkpatrick et al., 1996), none of the studies on the Deficit Syndrome looked at cannabis use in adolescence as a risk factor for a earlier age of onset (Di Forti et al., 2009, 2014) in non-deficit syndrome, or they merely excluded recent substance abuse (Bucci et al., 2016; Chang et al., 2013; Strauss et al., 2012; Allen et al., 2013).

This group of subjects constituted our control group of abstinent patients, and the findings suggest that their neuropsychological and early social deficits could underlay a profile of people at-risk to develop psychosis without the need for the additional risk factor of cannabis use (Di Forti et al., 2007).

3.2.2. Recreational Cannabis Users

As hypothesized, cases in this subgroup performed significantly better in IQ scores than never users, without no differences with everyday users. That means, better IQ reported in both cases and controls cannabis smokers is due to the subgroup of those who smoked cannabis less than everyday, thus accounting for the higher IQ reported in cannabis users overall. In fact, they generally represent the bigger proportion of smokers (Myles et al., 2016) and they accounted for the 48% of the control sample overall and for the 37.2% of the case sample in this study and for 52.2% of controls and 40.3% of cases in GAP study (see Chapter 4).

As expected, this sub-group of patients started with a better premorbid academic adjustment before their 12 years, that stayed stable between childhood and up to 16 years. Nearly after this period they tried cannabis for the first time (17.5 was the mean age and 16 the median age). In my knowledge, previous studies that explored premorbid academic conditions in psychotic patients cannabis users are rare and have selected only current or heavy users by comparing them with never users, thus revealing a worse pemorbid academic functioning (Compton et al., 2011; Sevy et al., 2010; Ringen et al., 2013).

The pattern of cannabis use in cases "less than everyday" users was not current in the 71.1% of them and mostly social (85%), but they still preferred high potency cannabis, they were mostly single and living with their parents. Neverthless, their educational/occupational trajectory seems to be better than other patients, in fact they have more years of education than never users and everyday users, they represented 37.2% of the proportion of cases that achieved a diploma, 46.6% of whom with a university degree and 43.5% of cases employed or student.

This group of patients, as expected, started also with a better premorbid sociability before their 12 years, that stayed stable between childhood and up to 16 years and this is, in my knowledge, the first study detecting this relationship by cannabis use. Leeson and colleagues, have found a better IQ (preserved in relation to premorbid IQ) in FEP cannabis recreational users in their lifetime compared to everyday users, but no differences in premorbid social adjustment (Leeson,

Harrison, et al., 2011). In another study, the same group found out that psychotic patients with preserved IQ showed a correlation between both premorbid or current IQ at baseline and social employment/occupational adjustment scale (using the Social Function Scale by Birchwood et al., 1990), but no other clinical feature distinguished the groups, including the level of premorbid social functioning measured by PAS (Leeson, Sharma, et al., 2011).

Among cases, diagnosis at first contact was important in determining the higher IQ of this subgroup of patients. Affective psychoses accounted for the higher IQ of cannabis recreational users, even after controlling for premorbid adjustment, and the difference with never users (both affective and non-affective) stayed significant even after adjusting for education and occupational status. We know that more affective features are associated with less cognitive impairment (Hill et al., 2013, 2008) in psychosis and a little proportion of schizophrenic patients appear indistinguishable from IQ-matched healthy controls (MacCabe et al., 2012). In an exploratory analysis, recreational cannabis users with non-affective psychosis were similar to non-smokers and everyday smokers in term of IQ and premorbid academic adjustment, but they were more sociable. In our sample, it seem more likely that the deficit in IQ is driven by the majority of cases, while the higher IQ is represented by a subgroup of mostly affective-psychosis with higher education and recreational cannabis use, which link with affective outcomes has been less evident in previous research (Moore et al., 2007).

Cases in this subgroup have also an intermediate age of onset (29.1±9.3), they are younger than never users but developed psychosis later than everyday users and started the use of cannabis at a later age than everyday users.

In controls, similarly to cases, the better IQ of cannabis recreational users accounted for the higher IQ of the cannabis-group and was associated with a better academic adjustment before 16 years, that stayed stable from childhood to early adolescence. In fact, group belonging became non-significant in determining the risk to be a recreational cannabis user or an abstinent subject in the multicomponent analysis, i.e. once inserted in a model considering IQ, premorbid adjustment and several other confounders, cases were not more at risk to be cannabis recreational

users than controls. They were also the group with more years of education and the most represented group among people with a university degree (51%) and having a job or a student position (50%).

They tried cannabis for the first time at a mean age of 18 years (most of them at 17 years, median age) and they mostly subsequently stopped its use (88.6%). Almost all of them (95.5%) smoked socially, sharing the substance with their friends. There were no differences in the type of cannabis preferred and they were more likely to have tried other drugs than everyday cannabis users. Allen and colleagues indicated in their meta-analysis that the influence of peers for cannabis use increases as the age of the participant increases (r =0.157) (M. Allen et al., 2003). All these data, taken together, suggest an explorative behaviour within a social context of friends, that is not capable to interrupt the trajectory of their life.

Additionally, given that these subjects are also more educated and the risk to become recreational cannabis-users in both cases and controls is higher for people with a university degree, we can speculate that they entered in contact with the substance during their academic career, that would be, in turn, responsible for their higher IQ, along with the higher occupational status (Dickens et al., 2001).

In fact, by performing the analysis with frequency of cannabis use as predictor and correcting for education, the effect of cannabis on IQ disappeared.

Looking at different scales of IQ, the risk to be a recreational user for both cases and controls augments with higher scores of Verbal Comprehension, that is a hold intellectual capacity related with premorbid IQ (O'Connor et al., 2012; Wechsler et al., 1981). A higher Perceptual Reasoning index (see also Coulston et al., 2007), that is also an index for executive functions (Wechsler et al., 1981) augments the risk to be a recreational cannabis user, and its effect is enhanced in people with a good premorbid sociability.

As already mentioned, Legleye and colleagues (2010) have found that adolescents that smoked cannabis with a recreational pattern of use, were less likely to drop out of secondary school and speculated that cannabis experimentation is very common among adolescents and may reflect successful peer integration and

thus a positive social experience that may, in turn, be protective for educational attainment (Legleye et al., 2010).

Another suggestion came from studies that relate anxiety and cannabis use (Buckner & Zvolensky, 2014; Foster et al., 2015, 2016), given that a link between higher IQ and anxiety in healthy subjects was proposed by Coplan and colleagues (Coplan et al., 2006, 2011). The majority of our patients (81.1%) and controls (71.5%) stated to have smoked cannabis (any pattern of use) to feel more relaxed and, if it would be of critical importance, it could suggest a common vulnerability to mood dysregulation in cases and controls, whit subsequent cannabis use propensity, where cases have additional genes susceptibility for psychosis.

Moreover, we know that anxiety and mood disorders are typical of the prodromal phase of schizophrenia (Howes & Murray, 2014), that in this subgroup of patients could be started at a later age, thus determining a later contact with the substance. However, we cannot test this hypothesis in our sample, we have only evidence of a relationship between affective psychosis, cannabis recreational use and higher IQ (Koenen et al., 2009; MacCabe et al., 2010).

These results, taken together, suggest that a good premorbid IQ, an early sociability and integration at school, coupled with higher education, could result in a better IQ, and this is not surprising. Cannabis or other-drug experimentation in this group seems to be just an incidental factor that could indicate their involvement in particular groups, thanks to the higher sociability (for example colleagues at university or during first level education), that prompted for cannabis use, but at a later age, thus reducing the risk to become everyday users, as later discussed.

3.2.3. Everyday Users

The IQ of everyday users, both cases and controls, was in an intermediate position between never users and less than everyday users and did not differ from any of the two.

As already mentioned, even if both cases and controls everyday users were more likely to be current users, not all everyday users were currently smokers, therefore

what we observed is unlikely due to an acute or residual cannabis effect. Additionally, the IQ of everyday cannabis users is a little higher than never users in our group (84.15±18.2 vs. 81.2±19.8 of never users) and the difference was even higher, but not significant, in a exploratory analysis where current cannabis users were removed (85.9±19.4 vs. 81.2±19.8 of never users).

Studies on abstinent (>28 days) cannabis abusing patients have found a better performance of these subjects in some domains (e.g. processing speed, working memory, executive functions) (Jockers-Scherübl et al., 2007; Schnell et al., 2009) but the lowest levels of schooling, although premorbid IQ was within normal limits and comparable to that of the non-abusers (Jockers-Scherübl et al., 2007).

Among cases and controls of our sample, everyday use, rather than non-use, was predicted by higher levels of perceptual reasoning (see also Coulston, Perdices, & Tennant, 2007) and verbal comprehension, which is a proxy for a higher premorbid-IQ (Wechsler, 1981). However, the risk to be a heavy cannabis user, rather than abstainers, was also augmented by a lower processing speed that resulted moderated by the protective role of a higher premorbid academic adjustment. This difference with previous studies, probably due to some residual effect of cannabis in this subgroup of patients (Jockers-Scherübl et al., 2007; Schnell et al., 2009) or to a premorbid condition that reduced the control on the substance (Wills et al., 2008).

The higher premorbid sociability and the lower premorbid academic adjustment that was observed in this group was also witnessed, along with less educational attainment and lower self-socioeconomic status, in cannabis abusers by Sevy et al. (2010) and, in poly-drug users, in a review by Larsen and collegues (2006).

Other studies found no association between premorbid scores and drug or cannabis abuse (González-Blanch et al., 2015; Rabinowitz et al., 1998; Van Mastrigt, Addington, & Addington, 2004) probably because they merely looked at PAS mean scores without any distinction between social and academic factor, thus losing the effect.

The risk factor constituted by a higher premorbid sociability and lower education is moderated by higher scores of working memory, that has been indicated as impaired in schizophrenia (Silver et al., 2003) and in cannabis users (Solowij and

Battisti, 2008), i.e. when working memory is higher, it reduces the probability to be heavy cannabis-users, rather than recreational-user, in cases and controls, even if they are more sociable or with an intermediate education (compulsory education or diploma instead of university degree). However, we don't know the causal direction of this relationship.

Thus, measures of cognitive control and executive functions have to be read in relationship with the moderator role of the early premorbid adjustment, probably in a two-way direction.

About controls, everyday users had a lower IQ than recreational users and no differences were found with never users (see also Grant et al., 2003; Schreiner & Dunn, 2012). As espected, everyday users had a lower academic adjustment before their 16 years (Apantaku-Olajide, James, & Smyth, 2014; Krohn, Lizotte, & Perez, 1997; Lee, Winters, & Wall, 2010) and a good early social adjustment (see also Kellam et al., 1980). Thus, cases and controls behaved very similarly in relation to everyday cannabis use, a part from the absolute difference in IQ and premorbid scores, that were lower in cases than in controls overall.

By summing-up, these results are more likely to be attributed to a complex mechanismn, involving several variables.

Cases and controls who became everyday smokers, had a significant drop in their academic functioning from childhood to first adolescence and it is possible to hypothesize that this could have affect the educational and occupational trajectory. Actually, 41% of cases with no education were everyday smokers and, in turn, having a lower education augmented up to 3 times the probability to be an everyday smoker than a subject with a university degree, regardless the group.

Everyday users were also more likely to be unemployed at the moment of the interview, compared to never users and less than everyday users, in case group but not in controls. In this latter group, lower education could have contributed in influencing their IQ, but not in impairing occupational and social functioning, also because it stayed in a normal range (mean IQ = 101±17.2).

In terms of sociability, while controls were not different in relationship to cannabis use and resulted in a slightly better adjustment in first adolescence than in

childhood, the opposite was true for cases. Cannabis smokers were more sociable overall, but everyday smokers developed a little deterioration in their premorbid social adjustment, during the period in which they started smoking cannabis, i.e. at their 15, that was the median age (15.6 mean age for controls; 16.1 mean age for cases) but these findings became non-significant according to Bonferroni's correction, thus it is possible to say that both groups stayed stable in their sociability. However, cases heavy users were more likely to have smoked cannabis alone, and to have used other drugs than less than everyday users and they were also more likely to live with their parents or in other families or institutions than never users and less than everyday users, despite the similar premorbid sociability with this latter group; thus they showed a more compromised functional adjustment than recreational users and never users, that perhaps started before the illness and that could be related to a more severe course of it (Caspari, 1999; Grech, Van Os, Jones, Lewis, & Murray, 2005; Linszen, Dingemans, & Lenior, 1994). They have also the lowest age of onset (Di Forti et al., 2014), at around 26 years.

Cases everyday smokers, but not controls, have preferentially chosen high potency cannabis and they referred that tolerance has increased their amount of cannabis used. In fact, the risk to be an everyday smoker was augmented by higher THC concentration-cannabis use, independently from group belonging.

The question is, if the drop in premorbid adjustment (greater at school) is a consequence of the pattern of cannabis misuse or the correlate of a prodromal phase with an earlier neurodevelopmental trigger for psychosis, that could lead in turn to an earlier and more persistent cannabis use, where genes have a crucial role.

Ringen and colleagues sustain the primacy of premorbid predisposition, that can affect both later cannabis use and neurocognition (Ringen et al., 2013). It was also suggested that a combination of genetic and environmental factors (e.g. parental substance use, Kirisci et al., 2009) is able to explain inclination to cannabis use that, in turn, influences the liability to affiliate with deviant peers (Gillespie et al., 2009) and that genetic factors play an increasingly important role during maturation in individuals' choice of peers, while early environment becomes less influential (Kendler et al., 2007). It was also suggested that poor self control (neurobehavioural

disinhibition), could lead to a specific and deviant peer environment – through cognitive distortions (Kirisci, Mezzich, Reynolds, Tarter, & Aytaclar, 2009) – which in turn mediates the relationship between neurobehavioural disinhibition and cannabis abuse (Feske et al., 2008).

Our cases and controls everyday smokers start with a worse premorbid academic adjustment in childhood, compared to never and recreational users, that became even worse in first adolescence, thus indicating an early and inexorable decline where cannabis is probably first selected, depending from predisposing factors (for example higher early sociability and/or poor self-control etc.), and after reinforced, by involving the subject in an even less challenging and stimulating world (see also Fergusson et al., 2003).

If cannabis use persists over time, the vicious circle can be maintained, thus gradually reducing both premorbid social (González-Blanche et al., 2015; Ringen et al., 2013) and academic adjustment and, consequently, IQ (Meier et al., 2012). In fact, as Salyers and Muser highlighted in their study, the better social skills of this group are not necessarly related to good interpersonal relationships (Salyers & Mueser, 2001).

4. Summary and Future Directions

Various risk factors play a role in individuals becoming heavy users, most of them related to the contact with the substance. Among cannabis everyday users, better premorbid conditions and peer influence might have triggered cannabis-use, as was probably true for recreational-users. However, heavy cannabis-users choose a high THC concentration-cannabis and they had an earlier age of initiation in its use and this might be responsible for the loss of control on the substance. In fact, risk-taking and sensation seeking behaviours are higher in males than in females and decline between adolescence and adulthood, possibly because of changes in the brain's cognitive control system, which improve individuals' capacity for self-regulation (Steinberg, 2008). Genetic factors, coupled with early environment,

could also have a role in poor self-control – i.e. executive functions – that could, in turn, explain other risk-factors as, for example, deviant peer affiliation, lack of coping strategies and more lifetime stress. On the other hand, good self-control could have protective effects through promoting better academic competence (see also Novak & Clayton, 2001; Wills et al., 2001, 2008; Wills & Stoolmiller, 2002). This complex interaction between predisposition and early cannabis abuse could have determined a different trajectory of life, by reducing the capability to achieve higher education, for example due to a lesser learning ability (that is the acute and residual effect of cannabis use), thus involving the individual in an even more poor environment and enhancing the risk to develop psychosis in people predisposed.

On the other hand, patients who smoked cannabis less than everyday seem to be the less vulnerable group, and further studies are required to clarify the role of recreational cannabis-use in the onset of psychosis in interaction with other risk factors as, for example, affective vulnerability or early traumatic experiences (Sideli et al., 2015). Both cases and controls with a recreational cannabis use exhibited a higher IQ and they also achieved a higher education level. If the hypothesis of a neuroprotective action of cannabis on a neurodegenerative process was true, we would have changed it into an "improving hypothesis", i.e. cannabis is able to enhance IQ, regardless any diagnosis of psychosis and in spite of the amount of experimental research that have demonstrate detrimental cognitive effects or no long term effects of cannabis on the brain. Finally, cases who never used cannabis represent the group more neurodevelopmental predisposed to psychosis (i.e. with a lower IQ and a higher social premorbid impairment), they have a stable poor functioning, a later onset of psychosis and a probably later deterioration in their academic premorbid adjustment. This group of patients, have not the same opportunity to enter in contact with the illegal substance and develop psychosis without the need of this additional risk factor.

In conclusion, these data suggest that premorbid cognition is greatly related to what we observe in people when a test is administered as adults. The long-term effects of cannabis use on cognitive functioning and IQ, that is «the global capacity of a person to act purposefully, to think rationally, and to deal effectively with his

environment» (Wechsler, 1939), take a larger route than the simple direct biological effect, due to the neuro-anatomic alterations related to heavy and earlier cannabis use (Lorenzetti et al., 2016); indeed, the final effect involves several aspects of an individuals' life, such as the failure in the academic achievement, preferred deviant friendships, subsequent lower socio-economic status, etc. (Rogeberg, 2013a) that could ultimately impair his cognition in the long term. Additionally, in vulnerable subjects, heavy cannabis use could multiply the risk of developing psychosis that, in turn, causes a further functional impairment, which starts in the prodromal phase and involves all the above mentioned areas and even more.

Future directions include further exploration of differences by gender and diagnosis, a deeper look to cannabis recreational-use and a cross exploration of the main findings in interaction with the polygenic risk score for psychosis.

5. Conclusions

The study confirmed that patients who used cannabis in their lifetime with a recreational pattern of cannabis use have higher IQ scores and a better and more stable premorbid adjustment than other patients. The study is also compatible with the view that the better premorbid social adjustment of patients with cannabis-use was responsible for the contact with the substance and that cannabis use increased the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability.

Taken together, these results are able to rule out the alternative explanation of a neuroprotective role of cannabis use on cognition, in favour of the hypothesis of a complex relationship between premorbid predisposition and different pattern of cannabis use in determining this paradoxical result.

If the trends of lower age at initiation of cannabis use and public acceptance of its use continue, along with a lack of information on these issues, a larger proportion of young people from the general population may develop cannabis abuse in the future with consequences that are not easily preventable.

6. Limitations and Strengths

The EU-GEI study has strengths, such as the large sample size, the differentiation of the sample across several countries, the reliability tests that were performed with researchers, and other strengths, as described in chapter 3.

At the end of this work I want to address some potential limitations that could be noticed in this study design.

Even if a prospective cohort study would be able to provide most robust design for establishing causal connections, in relation to psychosis, such a design is problematic, because psychosis is a rare disorder, with a large time lag between the occurrence of environmental adversities and the onset.

The case-control design framed into an observational epidemiological study, allows us to make comparisons of the prevalence of several exposures (putative risk factors) between a group of individuals who have the outcome of interest (in this case people affected by their first episode of psychosis) and a group of healthy people, with similar features to cases but without the disease of interest (controls) and representative of the general population. Case-control studies are easier and less expensive and time consuming than prospective cohort studies, because the disease has already occurred. They don't require large sample size unless the variable of exposure is very rare (Greenland, 2009) and have the advantage of allowing the study of several risk factors at the same time. Furthermore, the recruitment of a large multi-centre sample of incident cases of schizophrenia spectrum disorders and controls (such as EU-GEI) is able to provide an invaluable pool of subjects (with detailed clinical, environmental, and genetic data) from which is possible to detect even small effects for the values of interest (Annex I - "Description of Work, in www.eu-gei.edu).

I acknowledge that a case-control study may have some disadvantages such as selection bias if, for example the control group selected was not representative of the population, or it should represent the population at risk of the disease (i.e. they should be individuals who, if they had experienced the disease outcome, would have been included as cases in the study). Another source of bias is recall bias,

because the information about exposure to risk factors is collected retrospectively and people with the disease might be more likely to recall risk factors (Greenland, 2009) as, for example, could occur in PAS interview. However, one of the aims of the study was to ensure at least one corroborative source of information for each case (e.g. family, clinical notes, other clinicians etc.). Additionally, the predictive and concurrent validity of the PAS was supported in persons with schizophrenia by comparing it with both a similar but more elaborate retrospective measure and with data collected during late adolescence (Brill, Reichenberg, Weiser, & Rabinowitz, 2008). Socio-economic status in childhood could be a confounder in these analysis, difficult to be addressed as a unique index in a European study, where each country has a different meaning of its socio-economic distribution. However, Meier and colleagues tried to rule out the possible pre-morbid confounder of socio-economic status in adolescence and they still found an inferior educational achievement in cannabis users, especially if the use was persistent through the four years of their study (Meier et al., 2015). Everyday users in our study were also more likely to be unemployed at the moment of the interview, compared to never users and less than everyday users, in case group but not in controls. This suggests that the diagnosis of psychosis could be associated to a lower personal socio-economic adjustment, more than cannabis abuse *per se*.

We examined patients at their first episode of psychosis, which minimizes the influence from variables inherent to those with chronic illness and/or the effects of continuous pharmacological treatment on cognition. However, patients were not medication naïve and, as is well known, medication could have affected current neuropsychological performance (i.e. IQ) even in the short period between initial contact with the services and our cognitive testing. On the other hand, this could only be related to a flattering effect on the relationship between cannabis use and IQ, equally distributed among cases, that did not occur in this study, where IQ of cases and controls was similarly related to cannabis use. The big difference in everyday cannabis users between cases and controls could be due to the difficulty in involving people included in this subgroup from the general population. However, as already discussed in Di Forti et al. (2009), it seems unlikely that the difference in

frequency and type of cannabis used between cases and control group was driven by a recruitment bias.

Another point of concern could be due to the fact that cannabis use was self-reported. Nonetheless, as already mentioned, we had the opportunity to measure the reliability of the self-reported data on current users in a random sample of 56 cases from the GAP sample, by carrying out a urinary drug screening (UDS) and the accuracy of self-report data on current use in our sample was high. For obvious reasons, a history of lifetime use of cannabis cannot be assessed by a biological test.

Gurillo and colleagues (2015) have recently suggested that daily tobacco use could be associated with increased risk of psychosis and an earlier age at onset of psychotic illness. Even if it was not a goal of this study, it would have been important try to rule out its possible confounding effect, as was possible for other drug abuse in the lifetime and, since our information on tobacco use were limited, it was not feasible. However, tobacco current use was related to a lower IQ and this was not true for current cannabis smokers nor for cannabis lifetime users overall (any pattern of cannabis use); thus this two groups are not coincident, a part from early better sociability and lower worse scholastic adjustment as is true for patients with an earlier onset of psychosis, that was also detected in tobacco smokers (see also Gurillo et al., 2015).

Another limitation is due to the impossibility to look at symptoms dimension (i.e. negative and positive symptoms), due to the length in the cleaning effort of these data that is currently ongoing. Even if symptoms are not of principal interest in this work, they could have changed some results (for example IQ) or confounded specific analyses, even if the similarities of cases and controls in relationship to cannabis use let us to consider the possibility that symptoms are not so important in the relationship between the variables of interest. However, future directions of the study will have the opportunity to look at these aspects.

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Appendix I: MRC Sociodemographic Schedule 1-2

SCHEDULES FOR THE ASSESSMENT OF SOCIAL CONTEXTS AND EXPERIENCES

Full version

STUDIE: EU GEI	Date of Birth
Subject number: |__|EU|__|__| - |__|__|__|__|	|__|__|-|__|__|-|1|9|__|__|

MRC SOCIODEMOGRAPHIC SCHEDULE (Amended) Part 1

STUDIE: EU GEI	Date of Birth
Subject number: |__|EU|__|__| - |__|__|__|__|	|__|__|-|__|__|-|1|9|__|__|
Time interval: Present	Period – Replicat |0|__|-|0|__|
Interviewer:	Date |__|__|-|__|__|-|2|0|__|__|

1a. Subject is:

O1 Case **O2 Sibling** **O3 Control**

1. Gender O1 Male O2 Female

2. Age |__|__|

3. Ethnicity All Sites:

O1 White O2 Black O3 Mixed O4 Asian O5 North African O6 Other

4. Ethnicity Site Specific (UK)

O11 White British	O12 White Irish	O13 White gypsy, traveller	O14 Other White
O15 Mixed (w, bc)	O16 Mixed (w, ba)	O17 Mixed (w, as)	O18 Other Mixed
O19 Indian	O20 Pakistani	O21 Bangladeshi	O22 Chinese
O23 Other Asian	O24 Black Caribbean	O25 Black African	O26 Other Black
O27 Arab	O28 Other		

5. Place of Birth

O1 Austria	O2 Belgium	O3 France	O4 Germany
O5 Ireland	O6 Italy	O7 Spain	O8 Suisse
O9 The Netherlands	O10 Turkey	O11 United Kingdom	O12 Brazil
O13 Australia	O14 other, specify: _____		

6. **Age of migration (if applicable)** |__|__|

7. **Father's place of birth**

O1 Austria	O2 Belgium	O3 France	O4 Germany
O5 Ireland	O6 Italy	O7 Spain	O8 Suisse
O9 The Netherlands	O10 Turkey	O11 United Kingdom	O12 Brazil
O13 Australia	O14 other, specify: _____		

8. **Mother's place of birth**

O1 Austria	O2 Belgium	O3 France	O4 Germany
O5 Ireland	O6 Italy	O7 Spain	O8 Suisse
O9 The Netherlands	O10 Turkey	O11 United Kingdom	O12 Brazil
O13 Australia	O14 other, specify: _____		

9. **First language:**

O1 English	O2 German	O3 French	O4 Dutch
O5 Spanish	O6 Turkish	O7 Italian	O8 Kurdish
O9 Portuguese	O9 other, specify:_____		

10. **Ever employed** O0 No O1 Yes

11. Social class (Subject)

(provide descriptions only)	Current	Main
a. Job Title	_____	_____
b. What do (did) you mainly do?	_____	_____
c. What does/did organization make?	_____	_____

d. Social class subject:

O1 Higher grade Professional	O2 Lower grade Professional
O3 Intermediate occupations	O4 Small Employer and self employed occupations
O5 Self employed occupations	O6 Lower supervisory and lower technician occupations
O7 Lower services, sales and clerical occupations	O8 Lower technical occupations
O9 Routine Occupations	O10 Never worked and long-term unemployed

12. Social class Father (other_____)

(provide descriptions only)	Current	Main
a. Job Title	_____	_____
b. What do (did) you mainly do?	_____	_____
c. What does/did organization make?	_____	_____

d. Social class father:

O1 Higher grade Professional	O2 Lower grade Professional
O3 Intermediate occupations	O4 Small Employer and self employed occupations
O5 Self employed occupations	O6 Lower supervisory and lower technician occupations
O7 Lower services, sales and clerical occupations	O8 Lower technical occupations
O9 Routine Occupations	O10 Never worked and long-term unemployed

13. Mother's age at birth |__|__|

14. Father's age at birth |__|__|

15. Number of brothers and sisters |__|__|

16. Do you consider yourself to have (or ever have had) a hearing impairment? O0 No O1 Yes

17. Was the onset of the hearing impairment before the age of 18 years? O0 No O1 Yes

(Note for DATA ENTRY: open **EU_LIVPLA_PREV** and **EU_LIVPLA_CURR**: Living places previously and current)

18. Where have you lived during your life, starting with the place you were born?

No.	Country	City/Town	Street/Postcode	Age					Change of School	
				From			To			
1.									O0 No	O1 Yes
2.									O0 No	O1 Yes
3.									O0 No	O1 Yes
4.									O0 No	O1 Yes
5.									O0 No	O1 Yes
6.									O0 No	O1 Yes
7.									O0 No	O1 Yes
8.									O0 No	O1 Yes
9.									O0 No	O1 Yes
10.									O0 No	O1 Yes
11.									O0 No	O1 Yes
12.									O0 No	O1 Yes
13.									O0 No	O1 Yes
14.									O0 No	O1 Yes
15.									O0 No	O1 Yes

Current

No.	Country	City/Town	Street/Postcode	Age				
				From			To	
1.								

(Note for DATA ENTRY: open EU_MRC 2)

MRC SOCIODEMOGRAPHIC SCHEDULE (Amended) Part 1

1. **Since leaving your parents' home, have you lived with others?** O0 No O1 Yes

2. **Who do you live with…?(For b-d: Rate if age 17 or older at time; otherwise N/A not applicable)**

	Alone	Alone, with children	Partner, Spouse	Partner, Spouse, with children	Parents	Other family	Friends	Other: specify (e.g. hostel, halls of residence)	N/A
a) Now	O1	O2	O3	O4	O5	O6	O7	O8_____	O9
b) 1 yr ago	O1	O2	O3	O4	O5	O6	O7	O8_____	O9
c) 5 yrs ago	O1	O2	O3	O4	O5	O6	O7	O8_____	O9

3. **Do you own/ rent your home…? (For b-d: Rate if age 17 or older at time; otherwise N/A not applicable)**

	Privately owned (self)	Privately owned (family)	Rented (Private)	Rented (government)	Other, specify:	N/A
a) Now	O1	O2	O3	O4	O5_____	O6
b) 1 yr ago	O1	O2	O3	O4	O5_____	O6
c) 5 yrs ago	O1	O2	O3	O4	O5_____	O6

4. **Overcrowding**

	a) Now	b) 1 yr ago	c) 5 yrs ago
i. How many persons live(d) with you?	☐☐	☐☐	☐☐
ii. How many rooms in your home (exclude kitchen and bathrooms)	☐☐	☐☐	☐☐

5. **Have you ever had a long-term relationship (one year or more)** O0 No O1 Yes

6. **How many children do you have?** ☐☐

7. What is your relationship status …? (For b-d: Rate if age 17 or older at time; otherwise N/A not applicable)

	Single	Married, living with someone	In a steady relationship	Divorced, separated	Widowed	N/A
a) Now	O1	O2	O3	O4	O5	O6
b) 1 yr ago	O1	O2	O3	O4	O5	O6
c) 5 yrs ago	O1	O2	O3	O4	O5	O6

8. What is the highest level of education you have achieved?

O1	School, no qualifications	(to end of compulsory education; passed no exams, tests, etc.)
O2	School, with qualifications	(to end of compulsory education; passed one or more exams, tests, etc.)
O3	Tertiary, Further	(first level of non-compulsory education; e.g. A-levels, Baccalaureate)
O4	Vocational	(job related education, e.g. teacher training, plumber, electrician, etc.)
O5	Higher (undergraduate)	(University; first degree)
O6	Higher (postgraduate)	(University: higher than first degree level, e.g. Masters, PhD)

9. How many years have you been in education? (from beginning of compulsory education) |__|__|

10. Are you employed (paid work) …? (For b-d: Rate if age 17 or older at time; otherwise N/A not applicable)

	Unemployed	Economically inactive (i.e. house person, physical illness/disability, career, retired)	Student	Part-time employee	Full-time employee	Self-employed	N/A
a) Now	O1	O2	O3	O4	O5	O6	O7
b) 1 yr ago	O1	O2	O3	O4	O5	O6	O7
c) 5 yrs ago	O1	O2	O3	O4	O5	O6	O7

11. What is your monthly income …? (For b-d: Rate if age 17 or older at time; otherwise N/A not applicable)

		a) Now		b) 1 yr ago			c) 5 yrs ago		
i.	**Gross monthly income £**	_____		_____			_____		
ii.	**Income below median**	O0 No	O1 Yes	O0 No	O1 Yes	O3 N/A	O0 No	O1 Yes	O3 N/A
iii.	**Income below official poverty line**	O0 No	O1 Yes	O0 No	O1 Yes	O3 N/A	O0 No	O1 Yes	O3 N/A
iv.	**Receipt of welfare benefits**	O0 No	O1 Yes	O0 No	O1 Yes	O3 N/A	O0 No	O1 Yes	O3 N/A
	If YES, specify	_____		_____			_____		

12. What is your religious affiliation?

O0 None O1 Christian O2 Jewish
O3Muslim O4 Other, specify _____

13. How often do you attend religious services?

O0 Never O1 Once or twice a year O2 Monthly O3weekly

For first-generation migrants only

14. Where, on a scale from 1 to 10, do you rate your fluency in the majority language? |__|__|
(1=not fluent at all, 10= very fluent)

(Note for DATA ENTRY: open **EU_LTE, list of threatening events**)

Appendix II: OPCRIT Item Checklist

Opcrit for Windows (v4), Item Checklist.

Details & History

1	Source of Rating	(1-6)	
2	Time Frame	(1-4)	
3	Gender	(0,1)	
4	Age of onset		
5	Mode of onset	(1-5)	
6	Single '(subject never married / lived as married)'	(0,1)	
7	Unemployed at onset	(0,1)	
8	Duration of illness in weeks (max=99)		
9	Poor work adjustment	(0,1)	
10	Poor premorbid social adjustment	(0,1)	
11	Premorbid personality disorder	(0,1)	
12	Alcohol/drug abuse within one year of onset of psychotic symptoms	(0,1)	
13	Family history of schizophrenia	(0,1)	
14	Family history of other psychiatric disorder	(0,1)	
15	Coarse brain disease prior to onset	(0,1)	
16	Definite psychosocial stressor prior to onset	(0,1)	

Appearance & Behaviour

17	Bizarre behaviour	(0,1)	
18	Catatonia	(0,1,2)	
19	Excessive activity	(0,1,2,3)	
20	Reckless activity	(0,1,2,3)	
21	Distractibility	(0,1,2,3)	
22	Reduced need for sleep	(0,1,2,3)	
23	Agitated activity	(0,1,2,3)	
24	Slowed activity	(0,1,2,3)	
25	Loss of energy/tiredness	(0,1,2,3)	

Speech & Form of Thought

26	Speech difficult to understand	(0,1)	
27	Incoherent	(0,1,2)	
28	Positive formal thought disorder	(0,1,2)	
29	Negative formal thought disorder	(0,1,2)	
30	Pressured speech	(0,1,2,3)	
31	Thoughts racing	(0,1,2,3)	

Affect and Associated Features

32	Restricted affect	(0,1,2)	
33	Blunted affect	(0,1,2)	
34	Inappropriate affect	(0,1,2)	
35	Elevated mood	(0,1,2,3)	
36	Irritable mood	(0,1,2,3)	
37	Dysphoria	(0,1,2,3)	
38	Diurnal variation (mood worse mornings)	(0,1)	
39	Loss of pleasure	(0,1,2,3)	
40	Altered libido	(0,1,2)	
41	Poor concentration	(0,1,2,3)	
42	Excessive self reproach	(0,1,2,3)	
43	Suicidal ideation	(0,1,2,3)	
44	Initial insomnia	(0,1,2,3)	
45	Middle insomnia (broken sleep)	(0,1)	
46	Early morning waking	(0,1,2,3)	
47	Excessive sleep	(0,1,2,3)	
48	Poor appetite	(0,1,2,3)	
49	Weight loss	(0,1,2,3)	
50	Increased appetite	(0,1,2,3)	
51	Weight gain	(0,1,2,3)	
52	Relationship between psychotic and affective symptoms	(0,1,2,3)	
53	Increased sociability	(0,1,2,3)	

Abnormal Beliefs and Ideas

54	Persecutory delusions	(0,1,2)	
55	Well organised delusions	(0,1,2)	
56	Increased self esteem	(0,1,2,3)	
57	Grandiose delusions	(0,1,2,3)	
58	Delusions of influence	(0,1,2)	
59	Bizarre delusions	(0,1,2)	
60	Widespread delusions	(0,1,2)	
61	Delusions of passivity	(0,1,2)	
62	Primary delusional perception	(0,1,2)	
63	Other primary delusions	(0,1,2)	
64	Delusions & hallucinations last for one week	(0,1,2)	
65	Persecutory/jealous delusions & hallucinations	(0,1,2)	
66	Thought insertion	(0,1,2)	
67	Thought withdrawal	(0,1,2)	
68	Thought broadcast	(0,1,2)	
69	Delusions of guilt	(0,1,2,3)	
70	Delusions of poverty	(0,1,2,3)	
71	Nihilistic delusions	(0,1,2,3)	

Abnormal Perceptions

72	Thought echo	(0,1,2)	
73	Third person auditory hallucinations	(0,1,2)	
74	Running commentary voices	(0,1,2)	
75	Abusive/accusatory/persecutory voices	(0,1,2)	
76	Other (non affective) auditory hallucinations	(0,1,2)	
77	Non-affective hallucination in any modality	(0,1,2)	

Substance Abuse or Dependence

78	Life time diagnosis of alcohol abuse/dependence	(0,1)	
79	Life time diagnosis of cannabis abuse/dependence	(0,1)	
80	Life time diagnosis of other abuse/dependence	(0,1)	
81	Alcohol abuse/dependence with psychopathology	(0,1)	
82	Cannabis abuse/dependence with psychopathology	(0,1)	
83	Other abuse/dependence with psychopathology	(0,1)	

General Appraisal

84	Information not credible	(0,1)	
85	Lack of insight	(0,1)	
86	Rapport difficult	(0,1)	
87	Impairment/incapacity during disorder	(0,1,2,3)	
88	Deterioration from premorbid level of functioning	(0,1)	
89	Psychotic symptoms respond to neuroleptics	(0,1)	
90	Course of disorder	(1-5)	

Appendix III: CEQ and CIDI

Cannabis Experiences Questionnaire

STUDIE: EU GEI	**Date of Birth**
Subject number: |__|**EU**|__|__| - |__|__|__|__|	|__|__|-|__|__|-|**1**|**9**|__|
Time interval:	**Period – Replicat** |**0**|__|-|**0**|__|
Interviewer:	**Date** |__|__|-|__|__|-|**2**|**0**|__|__|

Instructions to researcher: *Please tick boxes as appropriate to indicate patient's responses. Please be reminded that some questions allow for more than one response.*

15.1 Have you ever smoked/used cannabis? O1 Yes O0 No

If answer is **NO,** *go to 15.17*

15.2 How old were you when you first tried cannabis? ..... ☐☐ years

15.3 Why did you first try cannabis? *(You can tick more than one box)*:

a) My friends were using it. O1 Yes O0 No
b) My family members were using it O1 Yes O0 No
c) To feel better (to get relief from either physical or psychological discomfort) O1 Yes O0 No
d) Other *(please explain) (not for data entry)* O1 Yes O0 No

_____

Instructions to researcher: *Please consider as current smokers all participants who report usually using/ smoking cannabis (incl. patients who have not smoked while inpatient/in prison and patients who report occasional use even if it is once every couple of years etc).*

15.4 Do you currently use cannabis? O1 Yes O0 No

If **Yes,** please answer *b,* if **No,** *go to 15.7*

b. If **YES**, why did you continue to use cannabis? *(You can tick more than one box)*:

a) I like the effect, it gives me a buzz O1 Yes O0 No
b) It makes me feel relaxed O1 Yes O0 No
c) It makes me feel less nervous and anxious O1 Yes O0 No
d) It makes me feel more sociable O1 Yes O0 No
e) Other *(please explain)* O1 Yes O0 No

_____

15.5 Would you like to stop using cannabis one day? O1 Yes O0 No

b. If yes, please explain *(not for data entry):*

_____

15.6 Does/did cannabis affect your health in any way O1 Yes O0 No

b. If yes, please explain *(not for data entry)*:

_____

15.7 If you are not a current user, how long ago did you stop smoking cannabis? ☐☐ months

b. Why did you stop? please explain *(not for data entry)*:

_____

15.8 How do/did you mostly use cannabis?

O1 I smoke/smoked it in a joint with tobacco
O2 I smoke/smoked it in a joint without tobacco
O3 I smoke/smoked it using a bong
O4 I eat/ate or drink/drank it
O5 Other (please explain): _____

15.9 How often do/did you use cannabis?

O1 Every day
O2 (More than) once a week
O3 A few times each month
O4 A few times each year
O5 Only once or twice

15.10 When do/did you mostly use cannabis?

O1 During the day
O2 During the evening
O3 During the day and evening
O4 At weekends
O5 During weekends and weekdays

15.11 Do you/did you mostly use cannabis:

O1 Socially (with friends)
O2 On my own

15.12 On average how much money per week do/did you usually spend on cannabis?

O1 Less than £2.50 (< €2.75)

O2 £2.50 - £5 (€2.75 - €5.50)

O3 £6 - £10 (€6.50 - €11)

O4 £11 - £15 (€12 – €16.50)

O5 £16 - £20 (€17.50 - €22)

O6 Above £20 (above €22)

15.13 What type of cannabis do/did you mostly use?

O1 Hash (cannabis resin/solid)

O2Imported herbal cannabis

O3Home-grown skunk/ Sensimilla

O4Super skunk

O5Other *(please state)*: _____

15.14. Why did you choose the above type? _____

15.15. How often have you had these experiences while smoking cannabis?

Please rate whether it was a good, bad or neutral experience. If rarely or never, ignore rating (good, bad, neutral) and go to next item.

	Rarely or never	From time to time	Sometimes	More often than not	Almost always	Good	Bad	Neutral
a) Fearful	O0	O1	O2	O3	O4	O1	O2	O0
b) Feel like going crazy/mad	O0	O1	O2	O3	O4	O1	O2	O0
c) Nervy	O0	O1	O2	O3	O4	O1	O2	O0
d) Suspicious	O0	O1	O2	O3	O4	O1	O2	O0
e) Feeling happy	O0	O1	O2	O3	O4	O1	O2	O0
f) Full of plans/ideas	O0	O1	O2	O3	O4	O1	O2	O0
g) Hearing voices	O0	O1	O2	O3	O4	O1	O2	O0
h) Able to understand the world better	O0	O1	O2	O3	O4	O1	O2	O0
i) Seeing visions	O0	O1	O2	O3	O4	O1	O2	O0

15.16 Life Time Cannabis History questionnaire

Instructions to researcher: *Please hand this section over to participant for completion. Explain to participant how to complete this part by using (a) as an example: If you were smoking cannabis when you were 15, were smoking 2-3 joints per day on average, you usually smoked hash and you only smoked by yourself.*

a) AGE RANGE: 0-11

i. Did you use cannabis between the ages of 0 and 11? O1 Yes O0 No

ii. Frequency

O1 Every day
O2 More than once a week
O3 About once a week
O4 About once/twice a month
O5 A few times a year
O6 About once a year
O7 I have only used cannabis once or twice

iii. Quantity *(average per day)*

O1 1 Joint
O2 2 or 3 Joints
O3 4 or more Joints

iv. Mostly shared O1 Yes O0 No

v. Type

O1 Hash (cannabis resin/solid)
O2 Imported Herbal cannabis
O3 Home-grown skunk/Sensimilla
O4 Super skunk
O5 Other (please state):_____

vi. Setting of use

O1 Socially (with friends)
O2 On my own
O3 Both

b) AGE RANGE: 12-16

i. Did you use cannabis between the ages of 12 and 16? O1 Yes O0 No

ii. Frequency

O1 Every day
O2 More than once a week
O3 About once a week
O4 About once/twice a month
O5 A few times a year
O6 About once a year
O7 I have only used cannabis once or twice

iii.	**Quantity** *(average per day)*	O1 1 Joint O2 2 or 3 Joints O3 4 or more Joints
iv.	**Mostly shared**	O1 Yes O0 No
v.	**Type**	O1 Hash (cannabis resin/solid) O2 Imported Herbal cannabis O3 Home-grown skunk/Sensimilla O4 Super skunk O5 Other (please state):_____
vi.	**Setting of use**	O1 Socially (with friends) O2 On my own O3 Both

c) AGE RANGE: ABOVE THE AGE OF 17

i.	**Did you use cannabis from the age of 17 onwards?**	O1 Yes O0 No
ii.	**Frequency**	O1 Every day O2 More than once a week O3 About once a week O4 About once/twice a month O5 A few times a year O6 About once a year O7 I have only used cannabis once or twice
iii.	**Quantity** *(average per day)*	O1 1 Joint O2 2 or 3 Joints O3 4 or more Joints
iv.	**Mostly shared**	O1 Yes O0 No
v.	**Type**	O1 Hash (cannabis resin/solid) O2 Imported Herbal cannabis O3 Home-grown skunk/Sensimilla O4 Super skunk O5 Other (please state):_____
vi.	**Setting of use**	O1 Socially (with friends) O2 On my own O3 Both

d) If your pattern of cannabis use has changed overtime, please state why? (not for data entry)

_____

e) Dependence screening for cannabis

Have you ever experienced 3 or more of the following characteristics?

		Lifetime		Last 12 months	
1.	Tolerance, as defined by either of the following:				
	a. A need for markedly increased amounts of the substance to achieve intoxication or desired affect.	O1 Yes	O0 No	O1 Yes	O0 No
	b. Markedly diminished effect with continued use of the same amount of the substance	O1 Yes	O0 No	O1 Yes	O0 No
2.	Withdrawal, as manifested by either of the following:				
	a. The characteristic withdrawal syndrome for the substance	O1 Yes	O0 No	O1 Yes	O0 No
	b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	O1 Yes	O0 No	O1 Yes	O0 No
3.	The substance is often taken in larger amounts or over a longer period than was intended	O1 Yes	O0 No	O1 Yes	O0 No
4.	There is a persistent desire or unsuccessful efforts to cut down or control substance use	O1 Yes	O0 No	O1 Yes	O0 No
5.	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	O1 Yes	O0 No	O1 Yes	O0 No
6.	Important social, occupational, or recreational activities are given up or reduced because of substance use	O1 Yes	O0 No	O1 Yes	O0 No
7.	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	O1 Yes	O0 No	O1 Yes	O0 No

15.17 Instructions to researcher: Please ask for each drug: ***Did you ever use?*** If **YES**, please continue the questions concerning current and past use. ***"Please also assess alcohol and drugs when applicable, (see separate Alcohol& Nicotine sheet)"***

[a] Dependence screening for any drugs:

1. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired affect.
    b. Markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the substance
    b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

[b] Definition 'Abuse'

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Recurrent substance-related legal problems
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

B. The symptoms

The symptoms have never met the criteria for Substance Dependence for this class of substance

Note for data entry: open **EU_CEQ_drugs** for each drug separately. Select the correct type of drug in the first question!

A. Inhalants, e.g. glue, petrol, gas……

1. Current use (< 12 months)

i.	**Used?**	O1 Yes	O0 No
ii.	**If YES: Used during last week**	O1 Yes	O0 No
iii.	**How many weeks over last 12 months?**	☐☐ Weeks	
iv.	**Frequency** *(i.e. mean use over weeks the substance was used)*	O1 Daily O2 Weekly O3 Less O0 Not applicable	
v.	**Dependence** [a]	O1 Yes	O0 No
vi.	**Abuse** [b]	O1 Yes	O0 No

2. Lifetime

i.	**How old were you when you first used inhalants?**	☐☐ Years old	
ii.	**Was there a time when you used them regularly?**	O1 Yes	O0 No
iii.	**How old were you when you used inhalants most regularly?**	From: ☐☐	To: ☐☐
iv.	**Frequency most regular period**	O1 Daily O2 Weekly O3 Less	
v.	**Dependence lifetime** [a]	O1 Yes	O0 No
vi.	**Abuse lifetime** [b]	O1 Yes	O0 No

3. If you are no longer using inhalants, when did you stop? ☐☐ Years old

4. Why did you decide to stop?

_____

B. Crack.....

1. Current use (< 12 months)

i.	**Used?**	O1 Yes	O0 No
ii.	**If YES: Used during last week**	O1 Yes	O0 No
iii.	**How many weeks over last 12 months?**	☐☐ Weeks	
iv.	**Frequency** *(i.e. mean use over weeks the substance was used)*	O1 Daily O2 Weekly O3 Less O0 Not applicable	
v.	**Dependence** [a]	O1 Yes	O0 No
vi.	**Abuse** [b]	O1 Yes	O0 No

2. Lifetime

i.	**How old were you when you first used crack?**	☐☐ Years old	
ii.	**Was there a time when you used them regularly?**	O1 Yes	O0 No
iii.	**How old were you when you used crack most regularly?**	From: ☐☐	To: ☐☐
iv.	**Frequency most regular period**	O1 Daily O2 Weekly O3 Less	
v.	**Dependence lifetime** [a]	O1 Yes	O0 No
vi.	**Abuse lifetime** [b]	O1 Yes	O0 No

3. If you are no longer using crack, when did you stop? ☐☐ Years old

4. Why did you decide to stop?

_____

C. **Cocaine**……

1. **Current use (< 12 months)**

i. **Used?** O1 Yes O0 No

ii. **If YES: Used during last week** O1 Yes O0 No

iii. **How many weeks over last 12 months?** [ ][ ] Weeks

iv. **Frequency** *(i.e. mean use over weeks the substance was used)*
O1 Daily
O2 Weekly
O3 Less
O0 Not applicable

v. **Dependence** [a] O1 Yes O0 No

vi. **Abuse** [b] O1 Yes O0 No

2. **Lifetime**

i. **How old were you when you first used cocaine?** [ ][ ] Years old

ii. **Was there a time when you used them regularly?** O1 Yes O0 No

iii. **How old were you when you used cocaine most regularly?** From: [ ][ ] To: [ ][ ]

iv. **Frequency most regular period**
O1 Daily
O2 Weekly
O3 Less

v. **Dependence lifetime** [a] O1 Yes O0 No

vi. **Abuse lifetime** [b] O1 Yes O0 No

3. **If you are no longer using cocaine, when did you stop?** [ ][ ] Years old

4. **Why did you decide to stop**?

_____

D. Amphetamines/stimulants, e.g. speed, ecstacy, ...

1. Current use (< 12 months)

i.	**Used?**	O1 Yes	O0 No
ii.	**If YES: Used during last week**	O1 Yes	O0 No
iii.	**How many weeks over last 12 months?**	☐☐ Weeks	
iv.	**Frequency** *(i.e. mean use over weeks the substance was used)*	O1 Daily O2 Weekly O3 Less O0 Not applicable	
v.	**Dependence** [a]	O1 Yes	O0 No
vi.	**Abuse** [b]	O1 Yes	O0 No

2. Lifetime

i.	**How old were you when you first used amph/stimulants?**	☐☐ Years old	
ii.	**Was there a time when you used them regularly?**	O1 Yes	O0 No
iii.	**How old were you when you used .... most regularly?**	From: ☐☐ To: ☐☐	
iv.	**Frequency most regular period**	O1 Daily O2 Weekly O3 Less	
v.	**Dependence lifetime** [a]	O1 Yes	O0 No
vi.	**Abuse lifetime** [b]	O1 Yes	O0 No

3. If you are no longer using amph/stimulants when did you stop? ☐☐ Years old

4. Why did you decide to stop?

_____

E. Sedatives, e.g. sleeping pills, valium (not prescribed by a doctor)

1. Current use (< 12 months)

i. Used? O1 Yes O0 No

ii. If YES: Used during last week O1 Yes O0 No

iii. How many weeks over last 12 months? ☐☐ Weeks

iv. Frequency *(i.e. mean use over weeks the substance was used)*

O1 Daily
O2 Weekly
O3 Less
O0 Not applicable

v. Dependence [a] O1 Yes O0 No

vi. Abuse [b] O1 Yes O0 No

2. Lifetime

i. How old were you when you first used sedatives? ☐☐ Years old

ii. Was there a time when you used them regularly? O1 Yes O0 No

iii. How old were you when you used sedatives most regularly? From: ☐☐ To: ☐☐

iv. Frequency most regular period

O1 Daily
O2 Weekly
O3 Less

v. Dependence lifetime [a] O1 Yes O0 No

vi. Abuse lifetime [b] O1 Yes O0 No

3. If you are no longer using sedatives, when did you stop? ☐☐ Years old

4. Why did you decide to stop?

_____

F. Opioids, e.g. heroin, morphine, methadone

1. Current use (< 12 months)

i. Used? O1 Yes O0 No

ii. If YES: Used during last week O1 Yes O0 No

iii. How many weeks over last 12 months? [ ][ ] Weeks

iv. Frequency *(i.e. mean use over weeks the substance was used)*

O1 Daily
O2 Weekly
O3 Less
O0 Not applicable

v. Dependence [a] O1 Yes O0 No

vi. Abuse [b] O1 Yes O0 No

2. Lifetime

i. How old were you when you first used opioids? [ ][ ] Years old

ii. Was there a time when you used them regularly? O1 Yes O0 No

iii. How old were you when you used opioidsmost regularly? From: [ ][ ] To: [ ][ ]

iv. Frequency most regular period

O1 Daily
O2 Weekly
O3 Less

v. Dependence lifetime [a] O1 Yes O0 No

vi. Abuse lifetime [b] O1 Yes O0 No

3. If you are no longer using opioids when did you stop? [ ][ ] Years old

4. Why did you decide to stop?

_____

G. Hallucinogens, e.g. LSD, mushroom, PCP

1. Current use (< 12 months)

i.	**Used?**	O1 Yes	O0 No
ii.	**If YES: Used during last week**	O1 Yes	O0 No
iii.	**How many weeks over last 12 months?**	☐☐ Weeks	
iv.	**Frequency** *(i.e. mean use over weeks the substance was used)*	O1 Daily O2 Weekly O3 Less O0 Not applicable	
v.	**Dependence** [a]	O1 Yes	O0 No
vi.	**Abuse** [b]	O1 Yes	O0 No

2. Lifetime

i.	**How old were you when you first used hallucinogens?**	☐☐ Years old	
ii.	**Was there a time when you used them regularly?**	O1 Yes	O0 No
iii.	**How old were you when you used ... most regularly?**	From: ☐☐	To: ☐☐
iv.	**Frequency most regular period**	O1 Daily O2 Weekly O3 Less	
v.	**Dependence lifetime** [a]	O1 Yes	O0 No
vi.	**Abuse lifetime** [b]	O1 Yes	O0 No

3. If you are no longer using hallucinogens, when did you stop? ☐☐ Years old

4. Why did you decide to stop?

_____

H. Ketamine

1. Current use (< 12 months)

i. Used? O1 Yes O0 No

ii. If YES: Used during last week O1 Yes O0 No

iii. How many weeks over last 12 months? [ ][ ] Weeks

iv. Frequency *(i.e. mean use over weeks the substance was used)*

O1 Daily
O2 Weekly
O3 Less
O0 Not applicable

v. Dependence [a] O1 Yes O0 No

vi. Abuse [b] O1 Yes O0 No

2. Lifetime

i. How old were you when you first used ketamine? [ ][ ] Years old

ii. Was there a time when you used them regularly? O1 Yes O0 No

iii. How old were you when you used ketamine most regularly? From: [ ][ ] To: [ ][ ]

iv. Frequency most regular period

O1 Daily
O2 Weekly
O3 Less

v. Dependence lifetime [a] O1 Yes O0 No

vi. Abuse lifetime [b] O1 Yes O0 No

3. If you are no longer using ketamine, when did you stop? [ ][ ] Years old

4. Why did you decide to stop?

_____

I. Other Drugs (e.g. mephedrone; legal highs):

Please specify: _____

1. Current use (< 12 months)

i.	**Used?**	O1 Yes	O0 No
ii.	**If YES: Used during last week**	O1 Yes	O0 No
iii.	**How many weeks over last 12 months?**	☐☐ Weeks	
iv.	**Frequency** *(i.e. mean use over weeks the substance was used)*	O1 Daily O2 Weekly O3 Less O0 Not applicable	
v.	**Dependence** [a]	O1 Yes	O0 No
vi.	**Abuse** [b]	O1 Yes	O0 No

2. Lifetime

i.	**How old were you when you first used ...?**	☐☐ Years old	
ii.	**Was there a time when you used them regularly?**	O1 Yes	O0 No
iii.	**How old were you when you used ... most regularly?**	From: ☐☐	To: ☐☐
iv.	**Frequency most regular period**	O1 Daily O2 Weekly O3 Less	
v.	**Dependence lifetime** [a]	O1 Yes	O0 No
vi.	**Abuse lifetime** [b]	O1 Yes	O0 No

3. If you are no longer using ..., when did you stop? ☐☐ Years old

4. Why did you decide to stop?

_____

Dependence screening for any drugs:

Have you ever experienced 3 or more of the following characteristics?

	Past		Present	
1. Tolerance, as defined by either of the following:				
a. A need for markedly increased amounts of the substance to achieve intoxication or desired affect.	O1 Yes	O0 No	O1 Yes	O0 No
b. Markedly diminished effect with continued use of the same amount of the substance	O1 Yes	O0 No	O1 Yes	O0 No
2. Withdrawal, as manifested by either of the following:				
a. The characteristic withdrawal syndrome for the substance	O1 Yes	O0 No	O1 Yes	O0 No
b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	O1 Yes	O0 No	O1 Yes	O0 No
3. The substance is often taken in larger amounts or over a longer period than was intended	O1 Yes	O0 No	O1 Yes	O0 No
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use	O1 Yes	O0 No	O1 Yes	O0 No
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	O1 Yes	O0 No	O1 Yes	O0 No
6. Important social, occupational, or recreational activities are given up or reduced because of substance use	O1 Yes	O0 No	O1 Yes	O0 No
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	O1 Yes	O0 No	O1 Yes	O0 No

[b] Definition 'Abuse'

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Recurrent substance-related legal problems
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

B. The symptoms

The symptoms have never met the criteria for Substance Dependence for this class of substance

Tobacco and Alcohol

STUDIE: EU GEI **Subject number:** |__|EU|__|__|-|__|__|__|__|	**Date of Birth** |__|__|-|__|__|-|1|9|__|
Time interval: 12 months	**Period – Replicat** |0|__|-|0|__|
Interviewer:	**Date** |__|__|-|__|__|-|2|0|__|__|

I would like to ask you about the use of tobacco.

Section Tobacco

1. *In the past 12 months* did you smoke or use for at least one month on a daily basis….

a) cigarettes or rolling tobacco?	O1 Yes	O0 No
b) cigars?	O1 Yes	O0 No
c) pipe?	O1 Yes	O0 No
d) snuff- or chewing tobacco?	O1 Yes	O0 No

2. *In the past 12 months,* how much … did you smoke/ use each day during the time that you smoked/ chewed tobacco most?

	No./day
a) cigarettes or rolling tobacco?	
b) cigars?	
c) pipe?	
d) snuff- or chewing tobacco?	

Appendix IV: WAIS-III Abbreviated Version

WAIS-III --- abbreviated version

Administration & Scoring Instructions

(Adapted from: Ryan et al. 1999)

STUDIE: EU GEI	**Date of Birth**
Subject number: | | EU | | |- | | | | |	| | |-| | |-| 1 | 9 | | |
Time interval: Present	**Period – Replicat** | 0 | |-| 0 | |
Interviewer: .....|	**Date** | | |-| | |-| 2 | 0 | | |

The shortened WAIS consists of the following subtests:

(i) Digit symbol substitution/ coding -- Complete
(ii) Arithmetic – Only the odd items
(iii) Block design – Only the odd items
(iv) Information – Every third item (6, 9, 12, 15, 18, 21, 24, 27)

Scoring instructions

To estimate the IQ, please follow these instructions:

- Calculate raw scores:
  - Arithmetic & Block design: total raw score * 2.
  - Information: total raw score *2.8.
- Transform into scales scores (per subtest), considering age.
- Calculate sum score of the 4 scaled scores.
- Sum score * 11/4 (=2.75) => WAIS estimation Total score
- Transform into IQ-estimate

(i) Symbol substation:	Total raw score (0-133)			Scaled score (0-19)	
(ii) Arithmetic:	Total raw score (0-22)			Scaled score (0	
(iii) Block design	Total raw score (0-68)			Scaled score (0	
(iv) Information:	Total raw score (0-28)			Scaled score (0	
WAIS-Total:	Sum scaled scores (0-76)			Estimate sum scaled scores (11/4* sum scaled scores)	

Estimate of total IQ (0-155): | | |

Digit Symbol - Coding- Administer according to standard procedures in the WAIS-III manual.

Arithmetic - Administration begins with item 5 and continues with every other item (i.,e., 5,7,9, 11, 13, 15, 17. 19). If perfect score is obtained on item 5, the subtest score is determined as follows: (a) sum points on items 5 through 19; (b) multiply this sum by 2; and
(c) add 4 points for items I through 4 that were not administered. If item 5 is failed, establish a basal in the usual was by administering items 1 through 4 in reverse order until two consecutive passes are obtained. Substitute the number of points earned on the basal items into step (c), if less than 4. Discontinue after two consecutive failures.

Block Design - Administration begins with item 5 and continues with every other item (i.e, .5, 7, 9, 11, 13). If perfect score is obtained on item 5, the subtest score is determined as follows:
(a) sum points on items 5 through 13; (b) multiply this sum by 2; and (c) add 8 points for items 1 through 4 that were not administered. If item 5 is either 0 or 1, establish a basal in the usual way by administering items 1 through 4 in reverse order until two consecutive scores of 2 are obtained. Substitute the number of points earned on the basal items into step (c), if less than 8. Discontinue after 2 consecutive failures.

Information - Administration begins with item 6 and continues with every 3rd item (6,9,12,15,18,21,24,27). If perfect score is obtained on item 6, the subtest score is determined as follows: (a) sum points on items 6 through 27; (b) multiply this sum by 3; and (c) add 4 points for items 1 through 4 that were not administered. If item 6 is failed, establish a basal in the usual way by administering items 1 through 4 in reverse order until two consecutive passes are obtained. Substitute the number of points earned on the basal items into step (c), if less than 4. Discontinue after 2 consecutive failures

Digit Symbol—Coding

Sample Items

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

1 1

EU GEI shortened WAIS-III Answer Sheet

STUDIE: EU GEI	**Date of Birth**
Subject number: | |EU| | |-| | | | | |	| | |-| | |-| **1** | **9** | | |
Time interval: present	**Period – Replicat** | **0** | |-| **0** | |
Interviewer :	**Date** | | |-| | |-| **2** | **0** | | |

1. Digital Symbol Coding

Time Limit	120 seconds
Completion Time	
Total Raw Score	(Maximum =133)

2. Arithmetic

	Problem	Time Limit (seconds)	Completion Time in Seconds	Correct Response	Response	Score (0 or 1)
	1	15		3		
	2	15		7		
	3	15		5		
	4	15		2		
Start→	5	15		£9.00		
	7	30		5		
	9	30		8		
	11	30		£10.50		
	13	60		£186.00		
	15	60		£600.00		
	17	60		£51.00		
	19	60		1 of 4 or 5 of 20		0 1 (11-60s) 2 (1-10s)
					Total Raw Score	

3. Block Design

EXAMINEE

Correct Design	Time Limit	Incorrect Design	Completion Time in Seconds	Correct Design	Score (Circle the appropriate score for each design.)
1. 	30"	Trial 1  Trial 2 		Y N	0 Trial 2: 1 Trial 1: 2
2. 	30"	Trial 1  Trial 2 		Y N	0 Trial 2: 1 Trial 1: 2
3. 	30"	Trial 1  Trial 2 		Y N	0 Trial 2: 1 Trial 1: 2
4. 	30"	Trial 1  Trial 2 		Y N	0 Trial 2: 1 Trial 1: 2
START 5. 	60"	Trial 1  Trial 2 		Y N	0 Trial 2: 1 Trial 1: 2
7. 	60"			Y N	0 16"–60": 4 11"–15": 5 6"–10": 6 1"–5": 7
9. 	60"			Y N	0 21"–60": 4 16"–20": 5 11"–15": 6 1"–10": 7
11. 	120"			Y N	0 66"–120": 4 46"–65": 5 31"–45": 6 1"–30": 7
13. 	120"			Y N	0 76"–120": 4 56"–75": 5 41"–55": 6 1"–40": 7

EXAMINER Total Raw Score

4. Information

	Item	Question	Response	Score (0 or 1)
	1	Saturday		
	2	Age		
	3	Ball		
	4	Months		
Start→	6	Sunrise		
	9	Brazil		
	12	Cleopatra		
	15	Olympics		
	18	Sistine Chapel		
	21	Water		
	24	Continents		
	27	Speed of Light		
			Total Raw Score	

Appendix V: Premorbid Adjustment Scale (PAS)

Premorbid Adjustment Scale (shortened version)

STUDIE: EU GEI	**Date of Birth**
Subject number: |__|__|__| - |__|__|__|__|	|__|__|-|__|__|-|1|9|__|__|
Time interval:	**Period – Replicat** |0|__|-|0|__|
Interviewer:	**Date** |__|__|-|__|__|-|2|0|__|__|

Instruction PAS (Premorbid Adjustment Scale) (to 16)

Source of information: patients and siblings + medical reports

Rate only the period prior to the first psychotic decompensation (with patients)

First rating: childhood to 12

Second rating: adolescence early: 12 to 16

1. Sociability and withdrawal

<12	12 - 16

0 Not withdrawn, actively and frequently seeks out social contacts.
1
2 Mild withdrawal, enjoys socialization when involved, occasionally seeks opportunities to socialize.
3
4 Moderately withdrawn, give in to daydreaming and excessive fantasy, may passively allow self to be drawn into contact with others, but does not seek it.
5
6 Unrelated to others, withdrawn and isolated, avoids contact.

2. Peer relationships

<12	12 - 16

0 Many friends, close relationships with several.
1
2 Close relationships with a few friends (1or 2), casual friendships with others.
3
4 Deviant (*unusual)* friendship patterns: friendly with children younger or older only, or relatives only, or casual relationships only.
5
6 Social isolate, no friends, not even superficial relationships.

3. Scholastic performance

<12	12 - 16

0 Excellent student

1

2 Good student.

3

4 Fair student

5

6 Failing all classes.

4. Adaption to school

<12	12 - 16

0 Good adaptation, enjoys school, no or rare discipline problems, has friends at school, likes most teachers

1

2 Fair adaptation, occasional discipline problems, not very interested in school, but no truancy or rare. Has friends in school but does not often take part in extracurricular activities.

3

4 Poor adaptation, dislikes school, frequent truancy, frequent discipline problem (*may have been suspended)*

5

6 Refuses to have anything to do with school – Delinquency or vandalism directed against school...

5. Social – sexual aspects

12 - 16

0 Started dating, showed a "healthy interest" in the opposite sex, may have "gone steady", may include some sexual activity.

1

2 Consistent deep interest in same-sex attachments with restricted or no interest in the opposite sex. flirtations.

3

4 Casual contacts with the same sex, no interest in the opposite sex.

5

6 Antisocial, avoids and avoided by peers.

Appendix VI: Schizophrenia Research 150 (2013)

Schizophrenia Research 150 (2013) 129–135

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Cannabis users have higher premorbid IQ than other patients with first onset psychosis

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ABSTRACT

Background: A number of studies have reported that patients with psychosis who use cannabis have better cognitive performance than those who do not. This is surprising as cannabis can impair cognition in healthy subjects. An obvious question is whether the better current performance of psychotic patients who have used cannabis is a reflection of their having a higher premorbid IQ than those psychotic patients who haven't used cannabis.
Aim: In a sample of patients at their first episode of psychosis, we tested the hypothesis that patients who smoked cannabis would have a higher premorbid IQ than patients who did not.
Methodology: 279 participants (119 patients and 160 healthy controls) were assessed in order to obtain current and premorbid IQ measures and detailed information on cannabis use. We examined the association between cannabis use and both premorbid and current IQ in patients and controls.
Results: Patients who had ever smoked cannabis had significantly higher current ($p < .001$) and premorbid IQ ($p = .004$) compared to patients who had never used cannabis. This difference was not found among controls.
Conclusions: These findings suggest that the better cognitive performance of patients with their first episode of psychosis who have used cannabis compared with those who haven't is due to the better premorbid IQ of the former.

1. Introduction

Cognitive impairment is a key feature of schizophrenia (Mohamed et al., 1999; Zanelli et al., 2010; Matheson et al., 2011) and also occurs, though to a lesser extent, in affective psychosis (Krabbendam et al., 2005; Kravariti et al., 2009). However, not all psychotic patients show cognitive impairment (Kremen et al., 2000). A recent epidemiological study of first-admission patients with psychotic disorders estimated that as many as 16% of schizophrenic, 20% schizoaffective, 42% of bipolar, and 42% of depressed patients may not be cognitively impaired (Reichenberg et al., 2009).

Cannabis use has been repeatedly shown to be a risk factor for the development of psychosis (Henquet et al., 2005; Moore et al., 2007; Potvin and Amar, 2008; Di Forti et al., 2009; Casadio et al., 2011). Three recent meta-analyses have reported that among patients with psychosis, those who have used cannabis show better cognitive performance than those who have not (Potvin et al., 2008; Yücel et al., 2010; Rabin et al., 2011). This is unexpected as it has been shown that cannabis use can impair cognition in healthy subjects (Fried et al., 2005; Meier et al., 2012).

Two different explanations have been advanced for this finding. The first suggests that those psychotic subjects who use cannabis have less premorbid cognitive impairment than those who do not. This could be because good premorbid functioning is necessary to acquire and sustain an illegal drug habit (Joyal et al., 2003; Stirling et al., 2005; Rodriguez-Sanchez et al., 2010) or because cannabis use increases the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability (Løberg and Hugdahl, 2009; Schnell et al., 2009; de la Serna et al., 2010; Yücel et al., 2010; Leeson et al., 2012; Schnell et al., 2012).

To our knowledge, only one recent study (Leeson et al., 2012) has found higher premorbid IQ in patients who smoked cannabis – among 99 FEP subjects – using the Wechsler Test of Adult Reading (WTAR) as an estimated measure of premorbid IQ. Other studies (Jockers-Scherübl

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et al., 2007; Sevy et al., 2007; DeRosse et al., 2010; Ringen et al., 2010; Yücel et al., 2010; Ringen et al., 2013) that have incidentally examined premorbid IQ in psychosis in relation to cannabis use have reported inconsistent findings, probably due to their small sample size and other methodological problems.

A second possible explanation, based on research into animal models of Parkinson's disease and Alzheimer's disease (Ramirez et al., 2005; Chung et al., 2011; Martìn-Moreno et al., 2011), suggests that some cannabinoids have a neuroprotective action which may help to prevent psychosis-related cognitive decline (Jockers-Scherübl et al., 2007; Løberg and Hugdahl, 2009).

We set out to test the first hypothesis (i.e. that patients who have smoked cannabis show a higher premorbid IQ compared to those who did not) in a sample of FEP patients. We did not expect to find any such relationship between cannabis use IQ and premorbid IQ in controls. This is the first study comparing the relationship of cannabis use to premorbid IQ, in a representative group of FEP patients, including those with affective psychosis, and a matched control group, whilst controlling for important social and demographic variables.

2. Methods

2.1. Sample

Data were derived from the Genetics and Psychosis (GAP) study (Di Forti et al., 2009; Mondelli et al., 2009; Aas et al., 2011; Di Forti et al., 2012; O'Connor et al., 2012), a case–control study of first-episode psychosis, conducted in consenting patients aged 18–65 years admitted to the South London and Maudsley Mental Health NHS Foundation Trust (SLaM). The study was approved by the local research ethics committee.

We collected data on cannabis consumption and neuropsychological performance from 279 subjects (119 patients and 160 healthy controls) recruited between February 2006 and June 2011. Characteristics of the sample are presented in Table 1. All subjects underwent an extensive assessment which included collecting information about their socio-demographic characteristics and lifetime substance use. Subjects were administered tests of premorbid and present intellectual level as soon as possible based on their compliance and within the first six months after their admission (instruments used are indicated below).

2.2. Patients

The 119 patients met ICD-10 criteria for psychosis (F10–19, F20–F29 and F30–F33) (WHO, 1992), 33 of them had a diagnosis of affective psychosis vs. 86 diagnosed as non-affective psychosis. Exclusion criteria were applied as follows: organic psychosis, acute intoxication (F1x.0), learning disabilities, history of traumatic brain injury and lack of English fluency.

Table 1
Socio-demographic characteristics.

	Cases	N	Controls	N	*t*-test or χ^2	df	p
Age in years, mean (s.d.)	29.6 (8.5)	119	29.6 (10.8)	160	0.03	277	.971
Males, n (%)	84 (70.6)	119	83 (51.9)	160	9.9	1	**.002**
Ethnicity, n (%)		111		159	16.8	2	**<.001**
White	33 (29.7)		95 (59.7)				
Black	55 (49.5)		47 (29.6)				
Other	23 (20.7)		17 (10.7)				
English mother tongue, n (%)	86 (72.3)	117	133 (83.1)	160	4.7	1	.052
Years of education, mean (s.d.)	13.2 (3.7)	108	15.1 (2.9)	147	4.1	200.1	**<.001**
Unemployed, n (%)	63 (59.4)	106	27 (22.0)	123	33.5	1	**<.001**

Abbreviation: df = degree of freedom.

2.3. Controls

Healthy controls (n = 160) were recruited from the same catchment area as the patients. Controls were recruited through local newspapers and internet advertising, job centres, hospitals and a pre-existing volunteer database. A control sample representative of the general population in age, gender, ethnicity and employment status was obtained (Di Forti et al., 2009). The Psychosis Screening Questionnaire (PSQ) (Bebbington and Nayani, 1995) was administered to exclude subjects who had any psychotic symptomatology.

2.4. Assessments

2.4.1. Demographic variables

A modified version of the Medical Research Council (MRC) Socio-demographic Schedule (Di Forti et al., 2009) was administered to all subjects. Ethnicity was self-ascribed during the interview and grouped into "white", "black" and "other".

2.4.2. Clinical assessment

Diagnoses for patients were established using the Operational Criteria Checklists (OPCRIT) (McGuffin et al., 1991), a 90-item checklist linked to a computerised diagnostic algorithm that includes a structured clinical interview with questions and optional probes derived from the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (SCAN, version 2.1) (WHO, 1999). It is capable of generating diagnoses under a number of classification systems such as DSM-IV and ICD-10. Diagnoses of non-affective psychosis included schizophrenia, delusional disorder, schizophreniform disorder, schizoaffective disorder depressed and schizoaffective disorder bipolar, whilst affective psychosis included manic episode with psychosis and major depressive episode with psychotic features. Levels of positive and negative symptoms were assessed by administering the Positive and Negative Syndrome Scale (PANSS), thus deriving scores for positive, negative and general symptoms (Kay et al., 1987).

2.4.3. IQ assessment

Current IQ was estimated based on five subtests (Information, Digit Span, Matrix, Block Design and Digit Symbol) of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997). Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR), a reading test normed with the WAIS-III, which is able to provide a broad estimate of general ability before the illness (Holdnack, 2001). WTAR has been shown to be stable in patients with traumatic brain injury (Green et al., 2008; Hanks et al., 2008) or exerting suboptimal effort (Whitney et al., 2010). Reading abilities are also widely used in order to infer premorbid IQ in psychosis, as related to measures of full scale IQ, verbal IQ, verbal comprehension (Hanks et al., 2008) and verbal memory (Whitney et al., 2010), the latter being more impaired than general IQ at first episode of psychosis (Mesholam-Gately et al., 2009). This discrepancy between verbal and non-verbal scores in psychotic patients (Wilk et al., 2005) has been shown in people with a genetic liability to develop schizophrenia (Kravariti et al., 2006).

2.4.4. Drug use assessment

By using the Cannabis Experience Questionnaire (modified version) (Di Forti et al., 2009), all subjects were assessed for lifetime cannabis use (used at least once), age at first use in years (then dichotomized according to mean age at first use), type of cannabis used most often (hash/imported herbal cannabis or – alternatively – skunk, high potency cannabis), frequency of use (everyday/less frequently), current use (customarily smoking cannabis/no), mode of use (social/isolated), self-estimated number of times that they used cannabis over the

Table 2
Pattern of cannabis use.

	Cases	N	Controls	N	t-test or χ^2	df	p
Ever used cannabis lifetime, n (%)	86 (72.3)	119	98 (62.0)	158	3.1	1	.074
Age in years of first use of cannabis[a], mean (s.d.)	16.4 (4.6)	82	16.1 (3.0)	98	0.70	135.5	.498
Current cannabis users[a], n (%)	34 (39.1)	87	36 (36.4)	99	0.1	1	.703
Frequency of use (everyday/less frequently)[a], n (%)	38 (48.7)	78	15 (17.0)	88	19.08	1	**<.001**
Type of cannabis used[a], n (%)		66		86	−4.59	1	**.045**
Hash and imported herbal cannabis	23 (34.8)		44 (52.4)				
Sinsemilla (skunk)	43 (65.2)		42 (28.8)				
Mode of cannabis use[a], n (%)		77		92	1.65	2	.437
Socially	49 (63.6)		67 (72.8)				
Isolated	13 (16.9)		12 (13.0)				
Both	15 (19.5)		13 (14.1)				
Number of times of cannabis use lifetime[a], n (%)		60		88	1.29	3	.730
Once or twice only–fewer than 10 times	12 (20.0)		14 (15.9)				
Between 10 and 50	3 (5.0)		7 (7.9)				
Between 50 and 200	9 (15.0)		10 (11.4)				
Over 200 times	36 (60.0)		57 (64.8)				
Ever used other illicit drugs lifetime, n (%)	51 (45.1)	113	53 (34.6)	153	3.0	1	.083
Drugs use (general), n (%)		119		158	4.66	2	.187
No drugs	33 (27.7)		60 (38.0)				
Only cannabis	37 (31.1)		45 (38.5)				
Cannabis and other drugs	49 (41.2)		53 (33.5)				

Abbreviation: df = degree of freedom.
[a] In those who had ever used cannabis.

lifetime (operationalized as described in Table 2) and lifetime use of other drugs (yes/no).

2.5. Statistical analysis

Chi-square (χ^2) tests and t-tests were used where appropriate to compare socio-demographic characteristics between cases and controls. Equality of variance was tested using Levene's test. A significance level of 5% (two-tailed) was initially specified; this was adjusted using a Bonferroni correction in the analysis of covariance (ANCOVA).

Estimated current IQ (WAIS) and premorbid IQ (WTAR) scores were compared between the groups, first using a t-test and then using ANCOVA to adjust for confounders in order to check if cases were lower in IQ and premorbid IQ than controls. Potential confounders were selected a priori based on the literature. In order to avoid overfitting the model, significance tests (Pearson correlations, t-tests and chi-squared tests) were used to select which of these to include in the ANCOVA. These included: gender, mother tongue, ethnicity and years of education (years attended school). Next, we stratified by group and used an independent two-tailed t-test to compare mean IQ and premorbid IQ between people with any lifetime cannabis use and those without, and also between different patterns of cannabis use (Table 2). This analysis was carried out in order to test the specific hypothesis that patients with *lifetime* cannabis use were better in their premorbid IQ. A 2 × 2 factorial ANCOVA was run (groups [cases, controls] × cannabis [cannabis yes, cannabis no]) controlling for covariates as specified previously; the inclusion of a cannabis by group interaction term formally tested whether the relationship between cannabis and IQ and premorbid IQ differed in cases and controls.

Finally, a score measuring the difference between current IQ and premorbid IQ (current IQ minus premorbid IQ) was calculated for the patient group only. We then carried out an ANCOVA using this score as the dependent variable and lifetime cannabis use [yes, no] as fixed factor, whilst additionally controlling for years of education and mother tongue (dichotomized as English vs. Not English first language), which a preparatory analysis showed to be related to differences between IQ and premorbid IQ. This analysis tested the hypothesis of a smaller difference between IQ and premorbid IQ in patients with cannabis use, compared with patients without any use of cannabis. Statistical analyses were carried out using SPSS 15.0 for Windows (SPSS Inc., 1994).

3. Results

3.1. Socio-demographic characteristics

Table 1 shows socio-demographic characteristics of patients and controls. There were no differences in mean age at assessment between cases and controls. Statistically significant differences emerged between patients and controls in gender (higher percentage of males in cases than in controls), ethnicity (higher percentage of black and other ethnic minority groups among cases) and years of education (fewer years of education among cases). The case group also contained a greater percentage of unemployed people at the time of assessment. All of these differences were expected (see also Di Forti et al., 2009) and, therefore, used as covariates.

3.2. Pattern of cannabis use

Table 2 reports patterns of cannabis use by group. All patients who reported use of cannabis in their lifetime started using cannabis prior to the onset of psychosis. There were no significant differences in ever having used cannabis or other illicit drugs between cases and controls. Among those who had used cannabis, there were no significant differences between cases and controls in age of first use, current cannabis use, context of use (isolated or social), or the number of times that they had used cannabis.

Statistically significant differences between cases and controls were, however, found in the type and the frequency of cannabis used. Cases were more likely than controls to have preferentially smoked "skunk" which has a relatively high concentration of Δ9-THC (12–18%) (Potter et al., 2008), and were more likely to have used cannabis everyday than controls. There were no significant differences between cases who used cannabis and those who did not in gender, age, ethnicity, years of education, mother tongue nor in any of the PANSS subscales: negative ($t(111) = -1.187$, $p = .238$), positive ($t(111) = .677$, $p = .500$) and general psychopathology ($t(111) = -.386$, $p = .700$) scores (data not shown in tables).

3.3. Current IQ and premorbid IQ in cases and controls

Differences between cases and controls emerged in terms of current IQ ($t(247) = 8.99$, $p < .001$) and premorbid IQ ($t(181) = 10.81$,

Table 3
Comparing IQ and premorbid IQ across different patterns of cannabis use.

	Cases			Controls		
	Mean (s.d.)	Mean (s.d.)	p	Mean (s.d.)	Mean (s.d.)	p
Cannabis use lifetime (yes/no)						
IQ	93.3 (11.0)	85.5 (10.1)	**<.001**	106.3 (15.1)	106.9 (17.9)	.838
Premorbid-IQ	91.2 (16.5)	79.1 (11.5)	**.004**	102.5 (10.2)	101.0 (10.9)	.518
Current use[a] (yes/no)						
IQ	91.6 (12.8)	90.6 (18.5)	.796	103.6 (17.5)	107.5 (13.4)	.223
Premorbid-IQ	91.6 (11.1)	94.7 (10.7)	.285	101.6 (10.7)	102.7 (10.1)	.659
Type of cannabis[a] (skunk/hash)						
IQ	88.8 (13.3)	93.0 (16.8)	.310	107.8 (16.0)	103.2 (13.9)	.118
Premorbid-IQ	93.2 (9.9)	92.8 (12.8)	.922	105.0 (9.2)	99.0 (11.9)	.069
Age first use in years[a] (>16/≤16)						
IQ	87.1 (15.3)	93.0 (17.3)	.154	112.3 (16.1)	103.8 (14.0)	**.016**
Premorbid-IQ	89.8 (10.2)	95.4 (11.4)	.075	104.7 (10.3)	101.3 (10.1)	.216
Mode of use[a] (alone/social)						
IQ	89.0 (9.5)	90.7 (17.2)	.745	105.0 (21.9)	107.0 (14.0)	.696
Premorbid-IQ	89.5 (10.0)	94.8 (11.3)	.172	101.3 (11.8)	102.4 (9.5)	.759
Frequency[a] (everyday/less freq)						
IQ	88.5 (14.3)	94.9 (16.1)	.086	109.1 (16.1)	105.1 (15.0)	.378
Premorbid-IQ	92.2 (11.9)	94.6 (10.5)	.582	101.5 (12.4)	102.3 (9.4)	.805
N. of times[a] (over/under 200 times)						
IQ	88.2 (14.6)	86.5 (16.7)	.691	106.8 (16.6)	103.3 (15.5)	.358
Premorbid-IQ	89.9 (10.6)	90.2 (12.2)	.925	103.5 (10.3)	101.0 (10.7)	.427

[a] In those who had ever used cannabis.

$p < .001$). Cases had a mean current IQ of 87.9 (16.2) and controls of 106.6 (16.2); cases had a mean premorbid IQ of 91.2 (11.3) compared with 102.0 (10.5) in controls. ANCOVAs were subsequently carried out adjusting for gender, years of education, mother tongue and ethnicity. Age was not included since WAIS scores and WTAR already take this into account. After adjusting for the above covariates, patients still performed significantly worse than controls in IQ ($F(1,233) = 53.1$, adjusted $p < .001$, $\eta^2 = 0.186$) and premorbid IQ ($F(1,169) = 27.0$, adjusted $p < .001$, $\eta^2 = 0.138$).

3.4. Association of IQ and premorbid IQ with cannabis use when stratifying by case/control groups

In cases, IQ ($t(104) = 3.6$, $p < .001$) and premorbid IQ ($t(81) = 2.9$, $p = .004$) were significantly higher among patients who had used cannabis compared with those who had never used it (Table 3). In contrast, in the controls there were no statistically significant differences either in IQ ($t(141) = -0.2$, $p = .757$) or in premorbid IQ ($t(98) = 0.6$, $p = .156$) scores between those who did or did not use cannabis. ANCOVAs adjusting for gender, education, mother tongue and ethnicity, still gave similar results in the case group for both IQ ($F(1,86) = 21.6$, adjusted $p < .001$, $\eta^2 = 0.201$) and premorbid IQ ($F(1,66) = 10.6$, adjusted $p = .002$, $\eta^2 = 0.139$) (not shown in table). We did not find any such significant differences when analysing the control group (all $p > .05$).

3.5. Patterns of cannabis use and IQ

T-tests in the group of lifetime cannabis users were only performed to establish whether current cannabis use, type of cannabis used, frequency of use, mode of use, number of times used or age at first use were associated with IQ or premorbid IQ. None of these variables were found to have a significant association with either IQ or premorbid IQ among cases or controls (all $p > .05$). We only found that controls who had smoked cannabis after age 16, had higher IQ than controls that had smoked cannabis earlier in life ($p = .016$) (see also Meier et al., 2012) (Table 3).

3.6. IQ and premorbid IQ scores association with cannabis use: Case–control comparisons

3.6.1. IQ

Factorial ANCOVA confirmed a significant main effect of the group (case/control) on IQ scores ($F(1,222) = 53.3$, $p < .001$, $\eta^2 = 0.205$). There was also a significant main effect of cannabis use ($F(1,222) = 8.1$, $p = .005$, $\eta^2 = 0.036$). The interaction effect between cannabis use and the group was significant ($F(1,222) = 13.7$, $p < .001$, $\eta^2 = 0.058$), indicating that the IQ of cases and controls was related differently to cannabis use. Specifically, the IQ of patients was significantly related to cannabis use ($F(1,86) = 21.6$, $p < .001$, $\eta^2 = 0.201$), whilst the IQ of the controls was not ($F(1,132) = 0.7$, $p = .399$).

3.6.2. Premorbid IQ

A factorial ANCOVA showed a significant main effect of the group (case/control) on premorbid IQ scores ($F(1,161) = 34.3$, $p < .001$, $\eta^2 = 0.176$), a main effect of cannabis ($F(1,161) = 6.2$, $p = .013$, $\eta^2 = 0.038$), and a significant interaction between cannabis and the group ($F(1,161) = 3.9$, $p = .048$, $\eta^2 = 0.024$) indicating that premorbid IQ of cases and controls was related differently to cannabis use. Whilst premorbid IQ of patients was significantly related to cannabis use ($F(1,66) = 10.6$, $p = .002$, $\eta^2 = 0.139$), premorbid IQ of the controls was not ($F(1,91) = 0.1$, $p = .730$).

3.7. Difference between IQ and premorbid IQ

A difference score was calculated (IQ minus premorbid IQ) for each of the patients. Those in the non-cannabis group were found to have a difference between premorbid IQ and IQ of 6.1 points greater (95% CI: 0.3, 11.7; $p = .037$) than that of patients who had used cannabis ($F(1,75) = 6.6$, adjusted $p = .012$, $\eta^2 = 0.081$).

Diagnosis had no effect in any of our analyses on cannabis use and IQ, or premorbid IQ score.

4. Discussion

The aim of this study was to test the hypothesis that among psychotic patients, those who had smoked cannabis would have a higher

premorbid IQ than those who had not. Our main finding was in line with this hypothesis and showed that patients who had used cannabis in their lifetime had higher scores in both IQ and premorbid IQ compared to those patients who had never used cannabis.

4.1. Why is lifetime cannabis use associated with better premorbid IQ?

In our sample of cases any lifetime use of cannabis was associated with a better premorbid cognitive performance, in line with reports by Yücel et al. (2010), Meijer et al. (2012), Rabin et al. (2013) and Schnell et al. (2012). Cognition has been established as a predictor of real-world community functioning in schizophrenia (Green et al., 2000; Evans et al., 2003) and 69% of our sample of psychotic cannabis users reported a social use of cannabis, a similar proportion as in controls. Thus, our findings are compatible with the view that, among psychotic patients, the better premorbid cognition of the group who had smoked cannabis is likely to have facilitated their use of the drug in a normal recreational way, sharing it with their friends. The findings are also compatible with the view that patients that used cannabis were less neurodevelopmentally impaired than those who did not. Other studies compatible with this latter view have reported that patients at their first episode who have used cannabis have fewer neurological soft signs (Ruiz-Veguilla et al., 2012) and less abnormal MRI scans (Cunha et al., 2013) than those who have not.

4.2. Are IQ and premorbid IQ of patients and controls different in relation to cannabis use?

Looking at differences between cases and controls, we found, as expected, significantly lower current and premorbid IQ in patients on the overall. We also expected that cannabis use would be associated differently with IQ and premorbid IQ in patients and controls. Among cases, cannabis use was associated with a higher IQ and premorbid IQ, whilst among the controls, there was no significant difference. Previous studies compared cases and controls who used cannabis at age 16 or before and their performance in single tests: Jockers-Scherübl et al. (2007) found an interaction effect of group and cannabis on the "digit symbol" subtest from WAIS-R. Yücel et al. (2010) reported that "visual memory", "working memory", and "executive functioning" were better in patients who used cannabis, but no interaction analysis was made with a corresponding control group. Meijer et al. (2012) found that lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition and face identity recognition, but they did not find any interaction effect with group status (patients, siblings and controls). To our knowledge, this is the first study that has investigated and found a relationship between IQ, premorbid IQ and cannabis use in cases but not in a comparison group of controls.

4.3. Difference between IQ and premorbid IQ in relation to cannabis use

As expected, the current IQ of patients was lower than their premorbid IQ on average (see also Dazzan et al., 2008). We calculated a difference score (IQ minus premorbid IQ) in order to see whether the estimated deterioration was associated with cannabis use (see also Leeson et al., 2011), and found this to be the case. This raises the possibility of a neuroprotective action of cannabis. However, those who used cannabis daily were neither less, nor more impaired than less frequent users; this was also the case when we compared patients that had started smoking cannabis at 16 or earlier (our mean age for cannabis use onset — the lowest age of first use in our sample was 5 years), and also when we compared patients that had smoked cannabis more or less than 200 times in their life, or patients that were currently smoking cannabis or not. Thus, we cannot make a definite statement on the question of any protective effect of cannabis use.

4.4. Limitations and strengths

We examined patients at their first episode of psychosis, which minimizes the influence from variables inherent to those with chronic illness and/or the effects of continuous pharmacological treatment on cognition. However, patients were not medication *naïve* and, as is well known, medication could have affected current neuropsychological performance (i.e. IQ) even in the short period between initial contact with the services and our cognitive testing. On the other hand, as already mentioned, WTAR – our main measure of interest – is also robust in patients exerting suboptimal effort due to medication effects.

The inclusion of a control group was another strength of our study, but, as some demographic differences show, our strategy of recruiting controls representative of the local population could have biased our findings. However, we corrected our analysis for these characteristics and differences in neuropsychological performances stayed significant. Otherwise, as already discussed in Di Forti et al. (2009), it seems unlikely that the difference in frequency and type of cannabis used between cases and control group was driven by a recruitment bias.

Cannabis use was self-reported but we measured the reliability of the self-reported data on current users in a random sample of 56 cases from the GAP sample, by carrying out a urinary drug screening (UDS). Of the 56 cases tested, 34 had reported they were not current users; 32 of these (88%) had a negative UDS, only 2 tested positive. Thus, the accuracy of self-report data on current use in our sample is high. For obvious reasons, a history of lifetime use of cannabis cannot be assessed by a biological test.

Finally, we are aware that reading-based tests have some limitations as a measure of premorbid IQ (Russell et al., 2000; O'Connor et al., 2012). However, WTAR is thought to be a more reliable measure of pre-morbid IQ (Green et al., 2008) compared to other tests like the NART (*National Adult Reading Test*) (Nelson and Willison, 1991) and is able to indicate a "hold" intellectual capacity (Cattel, 1971).

5. Conclusions

Our findings are in line with the hypothesis that among psychotic patients, cannabis users had a higher premorbid IQ than non-users (an association not witnessed among controls). Our cannabis-using patients also had a smaller difference between current IQ and premorbid IQ than non-using patients.

Kremen et al. (2008) point out that premorbid estimates should be understood as a measure of "potential" had a given subject not been destined to develop schizophrenia. Thus, individuals with a high premorbid IQ could be seen as less predisposed. Taking these findings together with the substantial evidence that cannabis use is a risk factor for psychosis, we suggest that cannabis may play a role in provoking psychosis in people who were less neurodevelopmentally impaired than is generally the case in psychosis.

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Contributors

Ferraro Laura: conception and design, analysis and interpretation of the data and draft of the article.

Robin M. Murray, Marta Di Forti, and Abraham Reichenberg: conception and design, revised the paper critically for important intellectual content and finally approved the version to be published.

Hannah Sallis helped with the analysis and interpretation of the data.

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Conflict of interests

They all have none to declare.

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